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VOLUME 15

MED

1953

PUBLISHED BY
ANNUAL REVIEWS, INC.
AND THE
AMERICAN PHYSIOLOGICAL SOCIETY

ON SALE BY
ANNUAL REVIEWS, INC.
STANFORD, CALIFORNIA, U.S.A.

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STANFORD, CALIFORNIA, U.S.A.

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FOREIGN AGENCIES

H. K. Lewis & Company, Limited
136 Gower Street, London, W.C. 1

The Maruzen Company, Limited
6 Tori-Nichome, Nihonbashi,
Tokyo

QP1
.A52
v. 15

PRINTED AND BOUND IN THE UNITED STATES OF AMERICA
BY THE GEORGE BANTA PUBLISHING COMPANY

PREFACE

In presenting this, the fifteenth volume of the *Annual Review of Physiology*, we wish first to express our great disappointment that Dr. Anton J. Carlson, who had accepted our invitation to write the Prefatory Chapter, found the task beyond his available resources of time and energy. We are certain our readers will share in this disappointment, for Dr. Carlson occupies among the elder champions of the discipline of physiology an unparalleled position of honor, respect and affection. In recognition of this, we present as our frontispiece a portrait of Dr. Carlson so that his shall not be missing from our accumulating gallery of distinguished physiologists.

The membership of the Editorial Committee has changed radically this year with the retirement of Dr. Frank C. Mann, Dr. John F. Fulton and Dr. Robert F. Pitts, whose wide contact with physiologists of the world has been of such great value in the choice of contributors. They will be sorely missed by those of us left to carry on this task. We particularly desire to acknowledge the valued leadership of Dr. Mann who, as Chairman of the Committee for the past few years, has preserved the continuity and guided the development of the *Review* with a devotion which can be fully realized only by those who have had the privilege of being his co-workers. He will be succeeded as Chairman by Dr. W. F. Hamilton. With the appointment to the Committee of Dr. J. P. Quigley of the University of Tennessee, the number of members will be reduced to five in conformity with the practice of the other publications of Annual Reviews, Inc.

A new chapter, that on the Higher Function of the Nervous System, makes its appearance in this volume under the authorship of Dr. H. F. Harlow. During the earlier years of the *Review* we carried a chapter on Physiological Psychology. This was later discontinued in the interests of conservation of space for the more central aspects of physiology when the *Annual Review of Psychology* was inaugurated. In recent years we have come to realize that a vast area of physiology, dealing with the integrated activities of the organism at a level higher than posture, locomotion and the like, was developing rapidly, yet escaping attention in the *Reviews*. Accordingly, we have instituted this new topic, in the conviction that the subjects of feeling, thinking, and doing, where they are accessible to physiological approach, are a proper, if not the crowning aspect of our science.

Finally we wish to thank all those who have contributed to the preparation of this volume, not the least of whom have been our editorial assistants, Bery Daniel, Jean J. Kaye, Carol F. Kupke, Suzanne Rebourgière, Lillian Rutherford, and Elinor Yount, for their loyal and painstaking service. Once again we wish to express our appreciation of the work of the George Banta Publishing Company in the preparation of this volume.

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VOLUME 16 (1954)

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ANTON J. CARLSON, M.D., PH.D.

TRANSPORT THROUGH BIOLOGICAL MEMBRANES

By Hans H. Ussing
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Introduction

The present review is intended to cover the period from June, 1950, to June, 1952. Lack of space, and also the late arrival in this country of certain journals, have made it impossible to prepare a complete bibliography of the topic for the period in question.

Papers not mentioned here may, however, be found in the reviews of neighboring fields, for instance Bioelectric Phenomena, Water Metabolism, Digestive System, Muscle, Peripheral Circulation, etc.

Diffusion and Active Transport of Strong Electrolytes

Much work has been devoted to the study of the peculiar distribution of K and Na between living cells and their surroundings. Extensive use of radioactive tracers for these ions has demonstrated that they penetrate more or less easily through nearly all cell membranes. Improved methods of chemical analysis, notably flame spectrometry, has led to the collection of a wealth of data concerning net ionic transfer rates under different conditions. Nevertheless it is often difficult to evaluate the experimental data in terms of physically meaningful parameters, such as true permeability constants, partial ionic conductances, or rates of active transport. The transfer rates by themselves tell nothing about the underlying forces. In order to decide whether ion movements occur passively or whether active transport is taking place, it is necessary to know the electric potential difference across the membrane as well as the ionic concentrations on either side of the membrane. It is therefore of great importance that the development of electrodes with a tip diameter of about 0.5 μ has made possible the measurement of potentials in many if not all animal cell types. The method which was first developed in Gerard's laboratory has been applied to study the relation between external potassium concentration and membrane potential of single muscle fibres [Ling & Gerard (1); Nastuk & Hodgkin (2)]. Elsner & J. W. Woodbury (3) have used a similar technique to study the resting and action potential of mammalian striated muscle *in situ*. L. A. Woodbury and collaborators have measured membrane potentials upon the embryonic chick myocardium (4), and stomach and intestinal epithelium cells of the frog (5). Békésy (6) reports the measurement of a resting potential inside the cochlear partition of the guinea pig. Weidmann has made similar measurements on *Sepia* axons (7) and single Purkinje fibres of the kid (8).

So far the results obtained have been in reasonably good agreement with

results obtained previously with more indirect methods. The cell interior has been found to be negative (usually between 50 to 100 mv.) relative to the outside medium. A new principle which, although indirect, gives correct values for the membrane potential of myelinated nerve fibres has been introduced by Huxley & Stämpfli (9).

It is to be hoped that the potential measurements will be extended to other cell types. In the case of the red cell and perhaps a few other cell types, reasonably good guesses can be made as to the magnitude of the membrane potential. For the vast majority of cell types, however, one has to resort to analogies, a procedure which is certainly dangerous.

As a leading principle, which is now shared by many, but apparently not all, workers in the field, the present reviewer shall consider it evidence for passive behaviour of an ion (*a*) if in the steady state it is distributed according to a Donnan equilibrium and (*b*) if the ratio between outflux and influx, as determined by isotopic tracers, equals the ratio between the electrochemical activities of the ion in the intracellular and extracellular phase, respectively. This relationship may be written: $M_{out}/M_{in} = (a_i/a_o)\exp(zEF/RT)$. M_{in} and M_{out} are influx and outflux, and a_i and a_o chemical activity of the ion in question in inside and outside medium, respectively. E is the potential difference across the membrane, and z, F, R, and T have their usual meaning. The basis of this relationship is discussed by Ussing (10, 11), Teorell (12) and Hodgkin (13). This equation is valid for passive ions irrespective of membrane structure and membrane charge. It is assumed that the ions are not subject to the drag of a rapid stream of water while crossing the membrane. As a criterion for passive behaviour of an ion, this equation has the advantage that it applies to cells not in equilibrium if the net changes are small relative to the total ionic exchange.

By the above-mentioned criteria, potassium seems to behave passively in nerve, striated muscle, and heart muscle. The sodium ions on the other hand, and Ca and Mg ions as well, are always present in much lower electrochemical activity inside nerve and muscle fibres than outside, and active extrusion of these ions therefore seems necessary for the maintenance of the composition of the protoplasm.

Some workers disagree with the general view taken here. Thus Shanes (14) states that "a nerve in apparent equilibrium with its environment achieves this by absorption of potassium at a rate exactly equal to the tendency of this ion to escape." Ling (15) has advanced a hypothesis according to which the ionic selectivity of the muscle cell is not a membrane property but "rather a result of the difference in magnitude of coulombic forces exerted upon various hydrated ions by spatially fixed charges." Both Shanes's and Ling's views seem to imply that the fact that a potassium ion enters the cell is sufficient reason for a sodium ion to leave.

Nerve and brain.—Keynes (16), using K^{42} as a tracer, found in the freshly dissected *Sepia* axon an average potassium influx of 11 $\mu\mu$mole/cm.^{2}/sec., and an average outflux of 33 $\mu\mu$mole/cm.^{2}/sec. The flux ratio thus was 0.33.

The flux ratio, as calculated from the membrane potential and the potassium concentrations by the above equation, was 0.35, in perfect agreement with the assumption of passive behaviour of potassium. Similarly for the 30 μ *Carcinus* fibres, Keynes & Lewis (17) obtained the flux ratio of 0.86 from the isotope experiment against 0.89 as calculated from potential and concentrations.

For sodium in the *Sepia* axon (16) the flux ratio was about 2. The calculated flux ratio for free diffusion of Na, on the other hand, was about 45. It thus seems that by far the greater part of the sodium outflux must be due to active transport.

Krebs, Eggleston & Terner (18) studied the turnover rate of potassium in brain slices and isolated retina, using K^{42} as a tracer. The turnover was taken to measure active potassium uptake and diffusion loss. In a later paper from the same laboratory [Davies & Krebs (19)], it is pointed out that the rapid exchange of K may possibly represent "exchange diffusion"; in other words, it need not be at all related to the work requirement for the osmotic maintenance of the cell. The cells lose K initially but are able to regain this ion if glucose and glutamate are supplied. Sodium migrates in a direction opposite to that of potassium and in approximately equivalent amounts. Unless the membrane potential of the nerve cells differs as to sign from the axons, it thus seems that the primary process might be the extrusion of the Na. *p*-Toluenesulfonamide reduces the rate of K accumulation. This is taken by the authors to indicate that carbonic anhydrase is needed to protect the cells against pH changes.

The reversible poisoning of nerve fibres by heavy metal ions has been studied by Castillo-Nicolau & Hufschmidt (20).

Hodgkin and collaborators have collected much additional evidence in favour of the sodium theory of nervous conduction. Reference has already been made to Hodgkin's very instructive article on the ionic basis of electrical activity in nerve and muscle (13), which gives the theoretical and experimental background of the theory. Perhaps the most striking new evidence comes from the measurement of the current-voltage relationship in the membrane of the giant axon of *Loligo* [Hodgkin & Huxley (21)]. By the aid of a negative feedback amplifier [Hodgkin, Huxley & Katz (22)], the membrane potential can be momentarily clamped at any desired level for a suitable period of time. If the potential is suddenly increased, very little current flows through the membrane. If the potential is clamped at a level lower than the normal, however, the fibre responds in a characteristic way, giving first an ingoing current lasting for about 1 msec., followed by a maintained outgoing current. The surge of ingoing current is reversed if Na in the medium is replaced by choline. The authors obviously identify the surge of ingoing current with the inflow of sodium ions, whereas the maintained outgoing current is assumed to be due to leakage of K. Huxley & Stämpfli (23) studied the effect of K and Na on resting and action potentials of single myelinated nerve fibres. Perhaps the most interesting observation was that the mem-

brane potential at the peak of the spike changed with Na concentration as if it were a diffusion potential across a membrane highly permeable to Na ions. During the spike, accordingly, Na behaves as a passive ion diffusing faster than any other ion in the system. Tracer experiments by Keynes (16) and estimation by activation analysis [Keynes & Lewis (24)] indicate that K leakage and Na entry during nervous activity in cephalopod giant nerves are of equal magnitude (around 3.5 $\mu\mu$mole/cm.^{2}/impulse).

Working with crab nerves, Shanes (25) has demonstrated that K released during stimulation is reabsorbed during recovery. The loss is increased by low concentrations of veratrine, which also increases the amount reabsorbed during recovery.

The problem as to whether the epineurium is a significant barrier to the diffusion of ions is still a matter of dispute. Using the ability of the nerve to conduct impulses as indicator of changes in the concentration of Na ions in the interstitial space of frog nerve, Lorente de No (26) made an estimate of the diffusion constant of Na in the epineurium. Based upon this value [compare also Gallego (27)] he concludes that the epineurium does not materially delay the loss of Na from the interstitial space to a Na free medium. Since conduction is retained under such conditions for a considerable period of time, he concludes that extracellular Na is unimportant for nerve function, whereas intracellular Na is involved in metabolic processes of importance for the function of the nerve.

Other methods than that applied by Lorente de No seem, however, to indicate that the epineurium has a very low permeability. Thus Crescitelli & Geissman (28) found that the sheath acted as an effective barrier against a number of antihistamines. The removal of the sheath does not damage the fibres since resheathed nerves behaved largely like normal nerves (29). Similar results were obtained by Feng & Liu (30). In this connection, it is of interest that Hoyle (31) has found the nerve sheath in the migratory locust to form an effective barrier between the high potassium concentration of the haemolymph and the much lower K concentration of the interstitial space of the nerve.

Muscle and heart.—Harris (32) and Keynes (33) have made determinations of the exchange rate of Na across the fibre membrane of the frog muscle fibre. The figures are in good agreement with previous determinations [Levi & Ussing (34)]. Harris (32) observed that if the washing out of Na^{24} from frog muscle is followed over several hours, the apparent Na flux across the fibre membrane often decreases with time. He suggests that this is due to the presence in muscle of three Na fractions, namely intercellular Na, intracellular Na, and Na adsorbed to the cell surface. Keynes (33) points out, however, that the deviation from exponential behaviour of the slow phase of Na exchange may arise from differences in size between the fibres.

Steinbach has presented additional evidence supporting the view that the Na loss from the fibres of frog muscles is due to active transport of this

ion (35, 36). Muscles enriched in Na and depleted of K were able to extrude Na and take up K in Ringer's solution (35), and even from a solution where most of the Na was replaced by choline (36). However, if the intracellular Na and part of the intracellular K were replaced by choline, no K uptake could take place afterwards, even from Ringer's solution. K uptake thus seemed secondary to Na extrusion.

Creese (37) has demonstrated that, in the isolated rat diaphragm muscle, all K exchanges at the same rate. Measurements after 5 to 9 hr. showed complete exchange. In bicarbonate-free Krebs saline at pH 7.5, the diaphragm lost 22 per cent of its K. When bicarbonate saline was restored at the same pH, the muscle K rose to normal values (38).

Sandow & Mandel (39) studied the effect of potassium and rubidium on the resting potential of muscle. It is concluded that the depolarization by KCl at the fibre surface is practically instantaneous. Under the assumption that Rb diffuses through the fibre membrane at a somewhat slower rate than K, the resting potential in the presence of these two ions had all the characteristics of a diffusion potential.

An increase of the resting potential of frog sartorius *in situ* during ether and ethyl urethane narcosis is reported by Rothschuh & Bogatzki (40). Fleckenstin *et al.* (41) have continued their studies on the interdependency between muscle contracture and membrane potential.

The distribution of Na and K between plasma and muscle in live animals under various conditions has been the subject of several investigations. In presenting the data, the assumption is often made that the fibres are free of chloride. Other workers prefer to consider the chloride ions as being distributed between intracellular and extracellular phase according to a Donnan equilibrium. For normal muscles, the two assumptions give essentially the same intracellular space. If, however, some experimental situation results in a decrease in the resting potential of the muscles, the two assumptions lead to rather different figures for the intracellular water phase and thus for the K and Na concentrations in the fibres. More data concerning membrane potentials and extracellular space are needed before it can be decided with certainty which of the above assumptions is the correct one.

The effects of electrolyte depletion and changes in blood bicarbonate on the distribution of muscle cation in the rat have been investigated by Cotlove *et al.* (42). Potassium deficiency and alkalosis are very similar in their effects, both giving a large increase in cellular Na and a drop in both intracellular and extracellular K. Acidosis has the opposite effect. Magnesium-deficient rats show only minor changes in cation distribution as compared with controls.

The characteristic interdependency between high blood bicarbonate, on the one hand, and potassium loss and Na gain by the muscles, on the other, has also been noticed by Muntwyler & Griffin (43). Electrolyte distribution following K-depletion and treatment with desoxycorticosterone acetate were nearly identical. Fuhrman & Crismon (44) studied the changes in mus-

cle electrolytes following ischemia. The resulting increase in intracellular Na was exceeded by the loss of intracellular K. This suggests that intracellular Na is more osmotically active than intracellular K. According to the authors the reason may be that part of the intracellular K is normally present in bound, osmotically inactive form [compare Elkinton (45)], or associated with larger anions exerting less osmotic pressure [Darrow (46)].

Epinephrine, according to Goffart & Perry (47), has a very peculiar effect on the potassium loss of rat diaphragm to K-free Tyrode solution. For about 10 min. the loss is diminished but then increases to attain a value several times that of the control. Similarly, the demarcation potential starts going up, but after some 16 min., drops below normal [Brown, Goffart, & Vianna Dias (48)]. In the cat's heart [Robertson & Peyser (49)] epinephrine injected intravenously brings about a substantial increase in intracellular Na and a drop in intracellular K. Assuming a "Conway distribution," the violent increase in water would be largely extracellular. However, the results might be interpreted as a large uptake of water and NaCl in the cells.

Erythrocytes.—Assuming the rapidly diffusing chloride ion to distribute between red cells and plasma water phases as a passive ion, the membrane potential of human red cells should be about 12 mv. [compare Hodgkin (13)]. On this basis, the concentration of red cell K should be 1.6 times the plasma concentration. Actually the concentration is much higher, and it thus seems that K must be actively transported into the cells, just as Na has to be transported out.

According to Ponder (50), red cells can accumulate K from isotonic mixtures of KCl and LiCl or of KCl and CsCl only a little less effectively than from mixtures of KCl and NaCl. K-accumulation thus is at least partly independent of the presence of Na. Much work has been devoted to the study of the exchange of Na and of K across the red cell membrance, using radioactive isotopes. Thus Raker *et al.* (51) found that 1.6 per cent of red cell K exchanges per hour at 37° C. Similar figures were obtained by Sheppard & Martin (52) and by Solomon (53). Q_{10} for the K exchange was found to be 2.2 (51) or 2.4 (52). According to Raker *et al.*, this is also the temperature coefficient of glucose utilization by the red cells. The K exchange rate is roughly proportional to the intracellular K concentration but largely independent of increased plasma concentration [Sheppard, Martin & Beyl (54); see also (51)]. All cell K seems to exchange at the same rate (51), although deviations have been observed (54). Deviations from simple exponential exchange have also been observed in the case of Na exchange (54). X-ray irradiation leads to loss of K and uptake of Na with little osmotic disturbance [Sheppard & Beyl (55)].

According to Lindvig, Greig & Peterson (56), the influx of Na^{24} and of K^{42} into red cells is decreased by 10^{-2} *M* acethylcholine. This treatment also delays hemolysis in isotonic $NaHCO_3$ solution. Other esters (e.g., triacetin) which are split by erythrocyte cholinesterase have similar effects [Greig & Holland (57)]. Inhibitors of cholinesterase like physostigmine counteract

the effect of acetylcholine [Holland & Greig (58)]. The effect of such drugs may be complex, however. Thus Christensen & Riggs (59) have found human and duck erythrocytes and Ehrlich mouse ascites carcinoma cells to concentrate physostigmine. K is lost from the cells in amounts about equalling the physostigmine uptake.

The active extrusion of Na and the uptake of K seem to depend on the same metabolic factors. According to Maizels (60), the cation transport can be energized by glucose mannose and fructose, but not by pyruvate and lactate. This and other pieces of evidence indicate that the ion transport in red cells is associated with glycolysis and not with respiration. The same conclusion has been reached by other workers.

The influx and outflux of Na in human erythrocytes has been studied by Harris & Maizels (61). Between pH 7 and 7.5 both influx and outflux are independent of pH. Below that region, both decrease, especially the outflux, and the cells gain Na. Above pH 7.5, both influx and outflux increase and more especially the influx, and again the cellular Na increases. Consequently cellular Na is at a minimum at about neutral solution.

The permeability of red cell ghosts to K and Na has been studied by Teorell (62). K penetrates faster than Na.

Frog skin.—The isolated frog skin is particularly well suited for the study of the active transport of sodium ions because it has turned out that, normally, active transport is solely reponsible for the well-known electric asymmetry of this organ. If the isolated frog skin, in contact with Ringer's solution on both sides, is "short-circuited" through an outer circuit of zero effective resistance, the current generated by the skin is identical with Na influx minus Na outflux [Ussing & Zerahn (63); see also Ussing (10, 64)]. Simultaneous determination of chloride influx and outflux, using the two isotopes Cl^{36} and Cl^{38}, demonstrate that chloride diffuses at the same rate in and out through the shorted skin and thus does not contribute to the electric current [Koefoed-Johnsen, Ussing & Zerahn (65)]. Experiments by Koefoed-Johnsen, Levi & Ussing (66) show that, in the nonshort-circuited frog skin, the flux ratio for chloride (influx/outflux) is that predicted from the potential difference and the chloride concentrations for a passive ion. The observations of identity between short-circuit current and active Na transport, as well as of the passive behaviour of chloride ions in the frog skin, have been confirmed by Linderholm (67). He was able to demonstrate further that the partial conductance resulting from sodium ions and that resulting from chloride ions sum up to give very closely the D.C. conductance of the skin. The short-circuit current, and thus the rate of Na transport, is increased by aminophylline (67) and by neurohypophyseal extract (63). In the nonshorted skin, neurohypophyseal extract increases the potential [Fuhrman & Ussing (68, 69)], also by a stimulation of the Na transport. Active Na transport was inhibited by dinitrophenol, thiocyanate, quinone, sulfanilamide, *p*-toluenesulfonamimide [Fuhrman (70)], and mersalyl (67).

During epinephrine stimulation of the frog skin, an additional source of

electric current is aroused, which could be identified with an active transport of Cl ions outward, presumably by the skin glands (65).

According to Huf & Wills (71), the active transport of NaCl across the isolated frog skin depends strongly on a sufficient amount of K being present in the solution. Rb almost completely, and Cs partly, substitute for K. Ammonium strongly inhibits the transfer of salt. Huf, Parrish & Weatherford (72) found an accumulation of H^+, K^+, and Ca^{++} at the outside of the skin concurrently with the uptake of NaCl and water through the epithelium.

Gastric mucosa.—Davies (73) has written a very stimulating review of older and newer literature concerning gastric secretion. Rather elaborate schemes with the object of explaining the formation of hydrochloric acid secretion have been advanced by Conway (74), Davies & Ogston (75), Rehm (76, 77; see also 78), and Nielsen & Rosenberg (79). Unfortunately space does not allow a discussion of the merits of the different mechanisms proposed.

The hypotheses of Davies & Ogston and of Rehm have in common the assumption of the transfer of electrons across some boundary in the gastric mucosa. Conway (74) points out that, as an alternative to the free electrons, the catalyst may itself diffuse or rotate in the membrane. The hypothesis of Nielsen & Rosenberg operates with the interesting possibility of an active absorption of OH^- ions from the secretion fluid by combination with a (hypothetical) organic metaphosphate, acting as a membrane carrier.

The presence of carbonic anhydrase in frog and toad gastric mucosa has been confirmed by Davies & Edelman (80). Complete inhibition of HCl production was produced, after a lag period, by $1.7 \times 10^{-2} M$ *p*-toluenesulfonamide and even lower concentrations of certain other inhibitors of carbonic anhydrase. According to the authors, this enzyme plays a role in maintaining acid base balance in the oxyntic cells. The role of urease in the gastric mucosa has been discussed by Glick *et al.* (81, 82, 83), Hastings *et al.* (84), and Martinson (85). Von Korff, Ferguson & Glick (83) conclude from the available data that the gastric urease has a protective function in providing NH_3 for neutralization of acid in particular histological regions. Thus neither carbonic anhydrase nor urease are immediately concerned with the formation of HCl.

Crane & Davies (86), working with isolated frog gastric mucosae, have performed estimations of the increase in respiration occurring during acid secretion. If the increase in the rate of respiration provides all power for secretion, the efficiency approaches 100 per cent. This assumption clearly is somewhat arbitrary. Thus Davenport & Chavre (87), studying the relation between substrate disappearance and acid secretion in mouse stomach *in vitro*, point out that stimulating substances qualitatively change the chemical reactions through which substrates feed into the secreting mechanims.

Radioactive tracers have been used by Mason & Bloch (88) and Gabrieli (89) to study the permeability of the stomach *in situ* to different ions. Hogben (90) has used tracers for Cl, Na, and K to investigate the contributions

of the corresponding ions to the short-circuit current of isolated frog gastric mucosa. It turned out that, with identical solutions on both sides of the mucosa, the current came quantitatively from the active transport of chloride ions. He assumes that the acid is formed from carbonic acid by forced exchange of chloride ions against bicarbonate ions. Actually experiments with C^{14}-labelled bicarbonate indicated an active transport of bicarbonate (or of CO_2) from the secretion side to the nutrient side (91). Thus the active anion exchange may be the fundamental process in the acid formation.

Teorell (92) has been able to demonstrate that the amount of base given off by the isolated frog mucosa to the nutrient solution is equal to the amount of HCl secreted. Under the conditions of the experiments (acid nutrient solution) the P.D. apparently was not related to the rate of secretion.

Gastric reabsorption of hydrogen ions is discussed by Friedman (93). The primary acidity of the gastric secretion has been discussed by Heinz (94). Calculations show that diffusion is much more important than flow in the passage of HCl from the gland cells to the lumen of the stomach. This is a result of considerable interest when we have to draw conclusions about the parietal cells from experiments on the whole mucosa. Gudiksen (95) has investigated the composition with respect to electrolytes of pure gastric juice from the cat.

Kidney.—Lack of space makes it impossible to discuss the extensive literature on urinary excretion of inorganic ions. The papers mentioned here are those immediately concerned with transport mechanisms.

Kidney slices, depleted of K, reaccumulate K under suitable conditions [Mudge (96, 97); Shideman & Rene (98); Davies & Galston (99)]. Simultaneously, there is an equally large extrusion of Na (99). As long as the membrane potential of the cells is unknown, it is impossible to decide whether both ions are transported actively, or whether the uptake of K is a consequence of the Na transport. In the latter case, the K turnover rate as measured with K^{42} by Davies & Galston (99) bears no relation to the work necessary to maintain the equilibrium concentration. The rate of K accumulation is augmented by a number of Krebs-cycle compounds (96, 99). Certain inhibitors, e.g. azide, $Cu,^{++}$ benemid, and theophylline depress K accumulation more than they do oxygen consumption (97). Inhibitors of carbonic anhydrase, cholinesterase and alkaline phosphatase had no effect (97). According to Stamler (100) the tubular transport mechanism for K and Na (which may or may not be identical with that responsible for K accumulations in the tubule cells), are not affected by either saturating the secretory mechanisms for carinamide, *p*-aminohippuric acid, or iodopyracet, or loading the resorptive mechanism for ascorbic acid or several amino acids. According to Berliner, Kennedy & Hilton (101), administration of maleate to acidotic dogs abolishes their capacity to excrete an acid urine. Malate had no effect on acid secretion by the isolated frog gastric mucosa. The relationship between acidification of the urine and potassium metabolism has been discussed by Berliner, Kennedy & Orloff (102; see also 103).

Other organs.—Bucher *et al.* (104) present data on the chemical changes

produced in isotonic solutions of NaCl and Na_2SO_4 by the small intestine of the dog. It seems that the intestine takes up Cl by exchange against bicarbonate. Blickenstaff *et al.* (105) found the Cl uptake from the jejunum of the dog to be independent of concentration within rather wide limits.

Rats receiving daily injections of desoxycorticosterone acetate excreted less Na in the feces than they did in control periods [Berger *et al.* (106)].

The permeability of the cornea to inorganic ions has been studied by Potts & Johnson (107) and Maurice (108). According to the latter investigator the corneal epithelium is extremely sensitive to mechanical stimulation, stirring of the solution in contact with it increasing its permeability to Na ions about five times.

The bicarbonate of the saliva of the rabbit has been found to originate largely in metabolic CO_2 (109). Flink *et al.* (110) have studied the changes in K and Na concentrations in liver slices accompanying incubation *in vitro*. The changes in potassium content of sea-urchin eggs accompanying fertilization have been studied by Malm & Wachtmeister (111) and Oddo & Esposito (112). Ramsay (113) has demonstrated that the malpighian tubules of mosquito larvae can excrete a fluid containing less Na than the haemolymph. There is no evidence that the tubules can ever excrete a fluid containing more Na than the haemolymph. Chloride ion regulation and oxygen consumption in a crab, *Ocypode albicans*, has been studied by Flemister & Flemister (114). Meyer (115) has studied the Na exchange across the gills of the goldfish. Schoffeniels (116) has used radiocalcium to study the uptake of this element in *Anodonta*.

Microorganisms.—Conway and associates (117, 118) have continued their studies on the potassium and hydrogen ion exchange in yeast. One important finding is that prolonged oxygenation before the fermentation greatly lessens the excretion of succinic acid. Under these conditions the excretion of hydrogen ions is accompanied by an uptake of K ions and an accumulation within the cells of extra HCO_3^- equivalent to about 80 per cent of the H^+ excreted. The acid secretion is inhibited by azide and dinitrophenol. Determinations of the intracellular pH of resting bakers' yeast cells by three different methods gives consistent values around 5.8 (119). There seems to be an outer region in yeast cells, readily accessible to Cl^-, K^+ and Na^+, but hardly accessible to succinate (120).

Malm (121) has found that weak acids with a dissociation constant about 10^{-4}, but not other acids, bring about loss of K from yeast cells. The factors influencing Na uptake in yeast are discussed by Scott *et al.* (122). Eddy, Hinshelwood, *et al.* (123, 124, 125) have studied the accumulation of alkali ions in bacteria.

Diffusion and Active Transport of Phosphate

Mueller & Hastings (126), studying the rate of transfer of phosphate across the red cell membrane, found the data consistent with simple diffusion. Gourley (127), on the other hand, interpreted his experiments in terms of an

initial esterification of phosphate in the cell membrane. Clarkson & Maizels (128) finally concluded from the distribution of enzymes in human red cells that phosphorylation cannot occur at the outer cell face and must therefore take place within the substance of the cell membrane or at its inner face. According to Holton (129), there is a relationship between the amount of phosphate that has entered the red cell and the block of bicarbonate penetration rate. Phosphate evidently exchanges less efficiently with bicarbonate than does chloride.

Using radioactive phosphate, Sacks (130), found a high rate of phosphate penetration into the liver. The data were consistent with the assumption of surface esterification [compare Popjak (131)], but do not exclude diffusion into the cells. In the brain (132), intravenously injected tracer phosphate becomes available to the brain substance by a slow secretion into the cerebrospinal fluid.

Experiments with isolated frog kidney indicated that the tubules are impermeable to phosphate in excess of that transferred by active transport [Hogben & Bollman (133)].

Diffusion and Active Transport of Nonelectrolytes

Sugars.—Rosenberg & Wilbrandt (134) have written a very instructive and stimulating review of enzymatic processes involved in cell membrane penetration. Most of the article is devoted to the penetration of sugars. The authors emphasize that several of the criteria often used to indicate active transport, like nonconformity with Fick's law, are in reality only indicative of "enzymatically controlled transport." Glucose penetration into erythrocytes [see also (135)] is an example of enzymatically controlled transport, which does not require work on the part of the cell. Both these authors and Le Fevre & Davies (136) favour the view that a carrier molecule participates in the passage of sugars through the erythrocyte membrane.

Levene *et al.* (137) have made the interesting observation that insulin makes possible the penetration of galactose into muscle without making this sugar available to muscle metabolism [see, however, (138)]. Sorbitol, on the other hand, does not penetrate into muscle whether or not insulin is given to the animals [Wick & Drury (139)].

Hele (140) found a parallelism between the absorption rates of different sugars in the gut and the rate at which they were phosphorylated by homogenates of intestinal mucosa with added adenosinetriphosphate. This observation is taken to indicate that a phosphorylation by adenosinetriphosphate is directly involved in the uptake. Whether inorganic phosphate is present or absent during intestinal glucose absorption seems of little importance [Larralde & Pons (141)].

Phlorhizin, while inhibiting the absorption in the gut of glucose, galactose, and possibly mannose, has no influence on fructose absorption [Bogdanove & Barker (142)].

Rothstein and co-workers have continued their studies on the effect of

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uranyl ion inhibition of glucose utilization in yeast. The uranyl ion in low concentrations preferentially inhibits the anaerobic utilization of hexoses. Aerobic metabolism is less sensitive to uranium (143). There are indications that the groups on the cell surface forming complexes with uranium are polyphosphates (144). The authors suggest (145) that enzymes on the cell surface bring about chemical changes in the sugar. Formation and dissociation of a carrier complex is not entirely ruled out.

Amino acids.—The distribution of free amino acids between plasma and human erythrocytes has been studied by Johnson & Bergein (146). The majority of amino acids showed equal distribution in both phases, whereas others were present in lower concentration in the cells than in the plasma. Christensen, Riggs *et al.* found considerable concentrating activity towards glycine and certain other amino acids in duck and human erythrocytes (147), rabbit reticulocytes (148), and Ehrlich mouse ascites carcinoma cells (149). Mature rabbit erythrocytes had no such activity (148).

Gibson & Wiseman (150), using specific enzymes for assaying D- and L-amino acids, found that those belonging to the L series are absorbed preferentially by the small intestine of the rat. The preference for L-amino acids is demonstrated even in the case of such that are foreign to the organism. The material does not indicate whether it is a case of true active transport or whether it is just "enzymatically controlled transport."

The permeability of brain slices to glycine and aspartic acid has been studied by Korey & Mitchell (151). Gale (152) has studied the accumulation of glutamic acid in bacteria.

Various compounds.—Ross (153) has performed quantitative studies of the permeability of the blood brain barrier in rabbits to a series of nonelectrolytes. The rates bear direct relationship to lipoid solubility as expressed by the ether/water distribution coefficient.

According to Franceschetti, Frommel & Jöhr (154), acetyl choline increases the permeability of the blood aqueous barrier to fluoresceine. Inhibition of cholinesterase seems to increase the permeability of the blood brain barrier to narcotics [Greig & Mayberry (155)].

The epithelium of the stomach and the ileum of Guinea pigs is impermeable to histamine [Dworetzky & Code (156)].

Permeability to Water

It has been emphasized by Jacobs (157) and Ussing (10) [see also Koefoed-Johnsen & Ussing (158)] that it is necessary to distinguish between two entirely different types of water permeability, namely osmotic (or filtration) permeability and diffusion permeability. The osmotic permeability is usually calculated from the rate of osmotic water transfer. The diffusion permeability, on the other hand, is obtained from experiments with isotopic water. In case water forms a continuous phase all through the membrane, the water translocation takes place mainly by laminar flow. As the pore size approaches molecular dimensions the rate of flow decreases until finally the rate of diffusion determines the passage of water through the membrane.

A comparison between osmotic permeability and diffusion permeability for water of a membrane therefore gives valuable information concerning the membrane structure. In the case where the two permeabilities are identical, we must conclude that water passes through by dissolving as single molecules in the membrane phase. It is of course imperative to express the two permeabilities in the same units, for instance cm./sec. Using data from the literature, Jacobs (157) calculated for the alga *Tolypellopsis* a filtration permeability which is about eight times higher than the diffusion permeability. Zeuthen & Prescott (159) have made simultaneous determinations of diffusion permeability and osmotic permeability on eggs of amphibians and fishes. The diffusion permeability was determined with heavy water by aid of the diver balance [compare Pigoň & Zeuthen (160)]. In the highly permeable ovarian egg of the frog, the osmotic permeability is much higher than the diffusion permeability, whereas in the fertilized egg the difference is less pronounced. For all the eggs studied, it is possible to assume that water passes exclusively through pores whereas the major part of the egg is impermeable to water. This would be in keeping with the observation made years ago by Krogh & Ussing (161) that the fertilized trout egg is absolutely impermeable to heavy water [Kusa (162) has observed that in heavy water Ringer the unfertilized trout egg shows a slight permeability to D_2O].

Løvtrup & Pigoň (163) used the diver balance to study the water diffusion permeability to D_2O and H_2O^{18} of the amoeba *Chaos chaos*. Both types of water give the same permeability constant (0.09 cm./hr.).

In 1935, Hevesy, Hofer & Krogh (164) demonstrated that the (apparent) osmotic permeability of the frog skin is greater than the diffusion permeability to water. This observation has been confirmed by Capraro *et al.* (165, 166, 167) for the isolated frog skin, and has been found to be even more pronounced in the toad skin [Koefoed-Johnsen & Ussing (158); see also (10)]. Both groups of investigators also found that the diffusion permeability to water is practically uninfluenced by posterior lobe hormones, whereas the latter increase the osmotic permeability by several hundred per cent. [Compare also Jørgensen (168) and Sawyer *et al.* (169, 170).] The posterior lobe effect may be due to active water transport (165) or to increased pore size (170), or to both phenomena.

The water diffusion permeability of the urinary bladder of the dog has been studied by Johnson *et al.* (171). D_2O was used as a tracer for water. The permeability constant was of the order of 4 cm./min. The osmotic water permeability was too small to be measured with certainty.

Osterhout (172) has found the permeability to water to be higher than that to ethyl alcohol in *Nitella*. The role of electroosmosis in living cells has been discussed by Blinks & Airth (173).

Permeability of Connective Tissue

It has been customary in discussions on permeability to place the emphasis upon the properties of the cell membranes. One of the lessons of recent years has been that the amount and structure of the hyaluronic acid and re-

lated compounds in the ground substance is a factor that cannot be ignored. The partial breakdown of hyaluronic acid brought about by hyaluronidase primarily affects the osmotic or filtration permeability to water. Instead of the filtration rate at constant pressure, the filtration pressure at constant infusion rate can be used to measure the effect of hyaluronidase [Lenstrup (174)]. Pores in mouse fascia, which have been opened up by hyaluronidase, are easily clogged by very dilute solutions of starch. Thereafter they can be opened again by ptyalin but not by hyaluronidase [Day (175)].

The relationship between ascorbic acid and skin permeability seems quite involved [see, for instance, Persson (176)]. Injected ascorbic acid decreases the spreading effect of hyaluronidase [Reppert *et al.* (177)] but, on the other hand, ascorbic acid itself is a spreading factor [compare Daubenmerkl (178)]. Theoretically interesting and also of practical importance is the discovery by Daubenmerkl (179) that dihydroxymaleic acid, which like ascorbic acid is a dienole, has a very powerful spreading effect.

Permeability of Capillaries

Wasserman & Mayerson (180) determined the exchange of albumin between plasma and lymph in dogs, using human and canine serum albumin labelled with I^{131}; 0.1 per cent of the albumin passed per minute into the intercellular space.

Radioactive tracers have been used by several investigators to study the exchange of ions across the capillaries. The transcapillary exchange of sodium has been studied in rabbits [Morel (181, 182)], guinea pigs, dog, man [Eichler (183)], rats [Sheatz & Wilde (184)], and normal and adrenalectomized dogs [Overman, Davis & Bass (185)]. Sheatz & Wilde also studied the transcapillary exchange of sulfate ions.

Most investigators have injected a tracer amount of the substance in question and followed the rate of disappearance of the radioactivity from the arterial blood. In order to evaluate this disappearance rate in terms of capillary permeabilities, the assumption is usually made that the limiting process in the equilibration between circulation and extracellular space is the passage of the ions through the capillary wall, whereas the distribution in the extracellular space is completed within a very short time. These assumptions have been contested by Pappenheimer *et al.* (186). Since the distance between capillaries is usually less than 50 μ, it can probably be accepted that great concentration differences cannot persist for any length of time in the direction perpendicular to the direction of blood flow. However, the length of the capillaries (of the order of 0.5 to 1 mm.) is such that equilibration by diffusion between the parts of the extracellular space adjacent to the proximal and distal end of the capillaries may require several minutes.

In the rabbit, the mixing between plasma Na and intercellular Na is practically completed in 5 min., and similar rates are observed in other experimental animals. Thus it is entirely possible that equilibrium within the extracellular space is not reached until there is also equilibrium between blood

and extracellular space. The complications arising from the uncertainty concerning the mixing in the extracellular space makes it, for the time being, difficult to use the tracer experiments for calculating absolute capillary permeabilities. Nevertheless tracer experiments of the type mentioned offer excellent opportunities for comparative studies of functional states of the capillary system.

The influence of steroid hormones upon capillary permeability is discussed in papers by Overman *et al.* (185) and Benditt *et al.* (187). Decourt & Ducrot (188) have studied the action of callicreine upon capillary permeability.

A highly important contribution to our understanding of capillary permeability is given in the paper by Pappenheimer *et al.* (186) mentioned above. From their own experiments on the filtration rate through the capillaries of the isolated hind limb of cats, and data from the literature, they conclude that the area through which filtration takes place constitutes only a minute fraction of the total capillary area. The permeation rate of solutes through the capillary wall is determined by the rate at which the venous pressure has to be changed in the perfused organ in order to counteract osmotic shrinkage, when the substance is suddenly added to the perfusion medium. By combination of the data of this "osmotic transient" with analyses of arterial and venous concentrations, the authors calculate permeabilities per unit area of the capillaries. The data so obtained are in agreement with the pore theory of capillary permeability. It seems that water and lipoid insoluble substances pass largely or solely through a number of pores which make up less than 0.2 per cent of the histological surface of the capillaries.

In order to carry through the calculations the authors have to make certain assumptions most of which seem perfectly sound. One of them, however, needs amplification. The authors state that "the same concentration difference which is effective in causing diffusion also gives rise to the observed osmotic pressure." The limitation of this statement can be most easily seen if the substance added to the blood is heavy water. Since heavy water and ordinary water diffuse at the same rate no osmotic transient can arise, although heavy water diffuses out of, and ordinary water into, the capillaries. Quite generally the osmotic transfer of solution is determined by the difference between the diffusion rate in the pores of the solvent and that of the solute. Only nonpenetrating substances exert the full osmotic effect.

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DEVELOPMENTAL PHYSIOLOGY[1,2]

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Each new individual as it develops attains its particular characteristics through the impress of its historical past. Its existence separate from the parent begins as a specialized reproductive cell or group of cells (egg, spore, bud, etc.) into which all of its potentialities for forming an organism like or similar to the parent are packed. Because of this very fact the reproductive unit would seem to be very complex. Indeed, the orderly progression of events by which its invisible (but demonstrable) complexity becomes visible is indicative of its essential preformation.

In normal development such reproductive or developmental systems depend to varying degrees upon proper external environmental conditions (food, water, oxygen, etc.) for the expression of their potentialities, in other words, for maintenance. However, the causal mechanisms which operate in bringing about the magnification and deployment of their preformed organizations are essentially independent of outside influences. In abnormal development (the material of experimental embryology), the revelation of latent potentialities in such processes as regulation and regeneration (the epigenetic properties of the germ) is in no way incompatible with the idea of the essential preformation of the germ.

The problem which confronts the student of developmental physiology is that of understanding how the progressively changing organization of the germ or reproductive unit is controlled. By what kinds of biochemical processes is the orderly progression of changes in chemical and structural makeup assured? Admittedly the problem is extremely difficult for we are attempting to explain the nature of progressive changes in a system when we know little about its origin (the elaboration of the reproductive unit) and its result (the adult individual). Furthermore, many attempts at analysis of the developmental process have been carried out on the mature reproductive unit (egg, sperm, spore, etc.) which in terms of biological potencies is apparently the most complexly organized stage in the life cycle of the organism.

The above introduction is designed to emphasize the importance of studies on the origin, nature, and localization of components of the egg (or other reproductive unit) and the changes in localization which accompany early stages of development. Both the particulate and nonparticulate (continuous) properties of the patterns of localized substances are receiving increasing attention in recent studies. An excellent example is the study of mitochondrial distribution in the sea urchin egg and its relation to developmental activities and to agents such as lithium and iodosobenzoic acid which rather

[1] The survey of literature pertaining to this review was concluded in June, 1952.

[2] The following abbreviations are used in this review: RNA (ribonucleic acid); and DNA (desoxyribonucleic acid).

specifically modify the developmental pattern [Gustafson & Lenicque (1)].

Recent contributions to our understanding of the physiology of development will be reviewed under the following headings which will serve to emphasize what the author believes to be important aspects of the problem: (*a*) formation and organization of the ovarian egg, (*b*) activation of the developmental system, (*c*) progressive changes in organization, (*d*) control of development, (*e*) expression of latent potentialities (regulation and regeneration), and (*f*) changes in metabolism during development.

FORMATION AND ORGANIZATION OF THE OVARIAN EGG

The increasing body of evidence for the important role which nucleic acids and nucleoproteins play in development has been ably reviewed by Brachet (2). Early work on the localization of nucleic acids was done with amphibians [Brachet, (3)] and has been extended by Dalcq & Seaton-Jones (4) to the oöcyte, egg, and early cleavage stages of various mammals. The fact that such biologically important substances as ribonucleoproteins are found to be localized in a definite pattern in early oöcytes of the rat, rabbit, mouse, and mole and the fact that this pattern coincides with the future planes of bilateral symmetry of the embryo [Jones-Seaton (5, 6); Dalcq (7)] are very interesting and suggestive. A further instance of the early polar localization of nucleic acids in amphibians has been described by Wittek (8). The relation of the axis of polarity of the egg to that of the parent has been demonstrated in the dogfish (9). Recent studies on yolk structure and its possible developmental role in the amphibian (10) and chick (11) have been reported. Earlier studies on the localization of various enzyme activities in eggs have been reviewed by Bradfield (12). More recently the presence of proteolytic enzyme activity in ovarian eggs of the clam (13) and cytochrome oxidase activity in the ovarian frog egg (14) has been demonstrated. In contrast to earlier studies, Osawa (15) has not been able to detect alkaline phosphatase activity in the oöcytes of *Triturus*.

Interesting studies by Johnston (16) show that the primordial germ cells of the largemouthed black bass are detectable early in development as an excresence at the dorsal lip of the blastopore, migrating later into the gonad primordium. The early setting aside (segregation) of these future reproductive units (the above being only one of many examples among animals) would seem to indicate their specialized nature. Consequently, more extensive and intensive studies of the origin and elaboration of the germ cells would appear to be a fruitful approach toward a solution of many of the problems of development.

ACTIVATION OF THE DEVELOPMENTAL SYSTEM

Contributions to our understanding of the general and cellular physiology relating to fertilization have been reviewed recently (17, 18). Studies on the interacting substances of egg and sperm have not been numerous (19, 20, 21), more attention having been paid to the activation changes within the cortex

of the egg itself (22, 23). The studies of Monroy & Runnström (24) constitute a first approach toward the isolation and characterization of sea urchin antifertilizin which seems to be localized in the pigment granules before fertilization, escaping from them during early stages of egg activation.

Of the very numerous and diverse changes in the physiology of the egg which accompany and are part of the activation process, the most interesting seem to be those concerning the egg proteins. Dohrn & Monroy (25) suggest that one of the first changes in the protein structure of the sea urchin egg is a breakdown of a cortical complex between the jelly-coat substance and nucleoprotein. Changes in the solubility and electrophoretic patterns of egg proteins have been described (26, 27). It may well be that the preformed, complex protein framework [cf. McCulloch (28)] of the mature egg undergoes, upon activation and early development, an orderly hydrolysis to smaller protein and amino acid products which are utilized for synthesis of new substances. The very interesting studies of Hoberman *et al.* (29) and Lundblad (30) constitute evidence in support of this view. Further studies of importance on nucleic acid and protein synthesis in early sea urchin embryos have been reported by Abrams (31) and Gustafson & Hjelte (32).

PROGRESSIVE CHANGES IN ORGANIZATION

Nucleic acid localization.—Progressive changes in the localization of cytoplasmic nucleic acids of the rodent egg during its cleavage and development up to the primitive streak stage have received careful study by Jones-Seaton (6). The morphogenetic importance of these basophillic substances has been pointed out (4, 5, 6). Minganti (33) has studied changes in RNA[2] distribution during early development of the snail (*Limnaea*). Segregation of cytoplasmic components into different cells during early development has long been recognized as one of the mechanisms of cell differentiation, but the recent studies of Lison & Pasteels (34) on the sea urchin show that there is also an unequal quantitative segregation of nucleic acid between the nuclei. In these unusually interesting and important studies, it was shown that the concentration of DNA[2] increases gradually during the first two cleavages, all the nuclei of the four-cell stage having the same concentration of DNA. However, in the formation of the eight-cell stage there is a segregation so that the DNA content in the nuclei of the lower quartet (future micromeres and macromeres) is greater than in the nuclei of the upper (mesomere) quartet. Further quantitative segregations of DNA between nuclei occur in the cutting off of the micromeres from the macromeres (32-cell stage) and in the differentiation of the ectoderm in the gastrula. The correlation of qualitative cytoplasmic segregation with quantitative nuclear segregation shown in these studies purports to be one of the most important discoveries in developmental physiology.

Antigenic changes.—A rather recent and apparently profitable method (because it deals with protein units) of approaching the problem of the nature of the progressive changes which occur during development concerns

the identification of the antigenic changes. The importance of these methods has been discussed in a review by Irwin (35) and also by Woerdeman (36). In her studies on the antigens of frog embryos, Cooper (37) continues to find antigens in the egg and neural plate which are represented by substances with immunologically related (but not identical) combining groups in adult frog's serum. The studies of Spar (38) on the frog show that the gastrula stage has various antigens which are: (*a*) present in the blastula, (*b*) peculiar to the gastrula, (*c*) present in the neurula but not in the blastula. Electrophoretic methods have been used by Flickinger & Nace (39) to demonstrate the development of new proteins in the frog egg.

Progressive changes in the antigenic specificity of the developing chick spleen (tested by its capacity to stimulate growth of host spleen when transplanted to host chorioallantois) have been described by Ebert (40). Two specific polysaccharide antigens of the spleen have been identified (41). In general, the studies of Ebert (42) show that antigenic substances identical, or closely related, to those of organs (heart, brain, spleen) of the adult chicken are present in the early chick blastoderm prior to the appearance of the corresponding organ primordia. Rather specific inhibition of the development of the brain and heart in blastoderms explanted to antibrain and antiheart sera containing media show that these antigens may be localized in definite areas of the blastoderm as early as the primitive streak stage. Similar specific inhibitory effects of antisera of frog gastrula ectoderm and archenteric roof on explants of the corresponding tissues have been described by Clayton (43). Ten Cate (44, 45) has shown that adult lens proteins are present in the lens vesicles of the 60-hr. chick and stage 21 (Shumway) frog embryos.

CONTROL OF DEVELOPMENT

The process by which structurally and physiologically different kinds of cells appear during development of the new individual is, of course, the major problem confronting the student of developmental physiology. Differentiation, as this process is usually described, should not be thought of as the origin of differences within an originally undifferentitated, simple system, but as the intensification and elaboration of complex differences already present, indeed, present throughout the life cycle of the individual. Two different kinds of differentiation processes are recognizable: (*a*) those which are segregative in character and (*b*) those which are environmentally controlled. By segregative differentiation is meant the progressive partitioning out (during cleavage or cell division) of the complex but orderly arranged, different, components of the germ to different cells. By environmentally controlled differentiation is meant the progressive and orderly appearance of different cell types through cell-cell interactions (direct cell-cell contacts and cell-hormone-cell interactions). Most examples of differentiation seem to involve varying combinations of these two basic types of mechanisms.

The Role of the Nucleus

A very significant question is that concerning the role of the nucleus in controlling either or both types of differentiation. Recent attention has turned to the study of the role of the nucleus in regulating the synthetic metabolism of the cell. Thus, in studies on amoeba, Brachet (46) has presented convincing evidence that synthesis of cytoplasmic particles containing RNA is under nuclear control, and Brachet (47, 48) and Mazia & Hirshfield (49) have shown that the nucleus plays a role in the coupling between oxidations and phosphorylations. On the other hand, Brachet (50) has found that in *Acetabularia* protein synthesis will continue up to five weeks after enucleation. Furthermore, studies on the uptake of labelled amino acids into proteins of cellular fractions of chick liver homogenates show the highest rate of incorporation in the microsomes and not in the nuclear fraction (51).

Whatever role the nucleus may play in the regulation of cellular metabolism, neither these studies nor those on development of anuran hybrids (52, 53, 54) give any indication that it plays a differential role in the control of differentiation processes. The studies of Moore (53) suggest that it is the cytoplasmic substrate on which the genes work which is different, not the genes themselves. A more direct and highly significant attack upon the problem has been made by Briggs *et al.* (55, 56). These workers injected the living nucleus from one of the blastomeres of a late blastula stage into the enucleated frog egg and found development of the egg to be perfectly normal. It seems then that the blastula stage nucleus is equivalent to the egg nucleus in so far as any role the nucleus may play in early differentiation is concerned. This is in contrast to the findings of Lison & Pasteels (34) in the sea urchin where quantitative nuclear differentiation (DNA content) occurs between the four- and eight-cell stage. A type of nuclear differentiation (in the macronucleus) which seems to be closely associated with morphogenesis in the protozoon, *Stentor*, has been described by Weisz (57, 58).

It is entirely possible that the nucleus and the genes may play their significant role in the control of normal development during the elaboration of the reproductive unit (formation of the germ cells) and not during the deployment of the preformed organization. This does not preclude the occurrence of abnormal development resulting from abnormal gene combinations (as in hybridization). Even the ageing of the sperm in the reproductive tract of the cock results in marked differential inhibition of development of hen eggs fertilized by such sperm. In these interesting studies by Dharmarajan (59), the head (brain) and tail regions are the most frequently abnormal regions.

Environmental Control

Obviously, the type of cell differentiation most susceptible to experimental analysis is that which seems to be environmentally sensitive. Recent contributions to our knowledge of environmental agents which play signifi-

cant roles in development will be considered in the following order: (*a*) Internal environmental control through cell-cell interactions (including induction and the role of developmental centers or organizers), and (*b*) external environmental agents (nutrition, oxygen, carbon dioxide, etc.).

Cell-cell interactions (*induction*).—The classical methods of demonstrating interactions between cells of the embryo by isolation, transplantation, or explantation of parts of the germ continues to be exploited with rewarding results. Among recent studies which deserve mention there are those of Hörstadius (60) on the sea urchin, Wilde (61, 62, 63) on interactions between the explanted gill and limb bud of the urodele, Lehman (64, 65) and Dalton (66, 67) on pigment cell behavior and differentiation in amphibia, and Holtzer (68) on the induction of muscles and skeleton by the transplanted spinal cord in amphibia. By the same methods the apparent absence of interactions controlling differentiation between the cells can be shown as, for example, in the pattern of neuroblast differentiation in the spinal cord of the 13- to 25-somite chick [E. Wenger (69); B. Wenger (70)].

Among the various types of cell-cell interactions those usually described as inductions may now be briefly considered. The role of the prechordal mesoderm in induction of the forebrain in amphibians has been reinvestigated by Gallera (71). The role of the medulla in inducing and controlling normal ear development has been demonstrated by Detwiler & Van Dyke (72, 73, 74) and Yntema (75). The time at which the reacting system becomes "attuned" to the inductor (i.e., becomes "competent") has been shown in the case of lens induction in *Amblystoma* to occur during the open neural fold stage [Liedke (76)]. The dependence of extrinsic eye muscle development upon the optic cup and the independence of the lids and lacrimal glands have been shown by Amprino (77, 78). Suggestions that both the ectoderm and the underlying mesoderm interact in controlling the type of feather differentiation in the chick wing bud are found in the studies of Saunders (79, 80, 81) and Cairns (82).

In the development of the nervous system one may find some of the most striking examples of cell-cell interactions. Since most of these have been presented in recent excellent reviews by Sperry (83) and Hamburger & Levi-Montalcini (84), only the general picture will be presented here. Peripheral nerve specificity or differentiation seems to occur as a result of nerve-end organ connections, the nerves being essentially indifferent prior to end organ contact [cf. the experiments of Miner (85) on rotation of tadpole skin strips]. The peripheral determination of central associations thus seems to be the means by which orderly patterns of fiber connections between the nerve centers and the appropriate end organs are established. Some of the cytochemical aspects of this inductive action of the periphery on indifferent neurons have been reported by Barron & Mottet (86). These investigators find that the concentration of DNA, RNA, and acid phosphatase in the neurons is regulated by the peripheral field (limb bud extirpation in chick embryos). Boell & Shen (87) find that choline esterase activity in the optic

lobe of the frog is correlated with the ingrowth of optic nerve fibers. Kupfer & Koelle (88) find that choline esterase is localized on the muscle nuclei of the rat four days prior to formation of the motor nerve endings.

Hormones and diffusible substances.—The role of hormones in the control of development is well established in the case of sex differentiation. In a recent colloquium on sex differentiation in vertebrates (89), the many different aspects of this problem were extensively reviewed. Consequently, the interested reader is referred to the published reports and their extensive bibliographies, and only a few recent examples of hormone control of development, not included in these reviews, will be mentioned here.

In the chick embryo, injection of 0.025 μg. of thyroid hormone seems to increase oxygen consumption, growth rate, and speed of development (90). In the zebra fish, on the other hand, thyroxin retarded pigment formation and morphogenesis in concentrations as low as one part per million (91). A related substance, tyrosine, has been shown by Morback & Saunders (92) to stimulate the growth of feather germs in explants of chick skin and through this means to bring about indirectly an increase in number of melanophores in the cultures. An apparently similar indirect influence of the thyroid hormone on melanoblast differentiation in the brown leghorn has been reported by Trinkaus (93).

Somewhat obscure cell-cell interactions which, nevertheless, are apparently mediated by diffusible chemical substances have been reported by Rose (94) in studies on the transmission and modification of renal to cartilage carcinoma from *Triturus* to the frog, and by Rose (95) in transplantation experiments with the hydroid coelenterate, *Tubularia.*

Perhaps the best examples of the role of diffusible chemical substances in the control of cellular differentiation are provided by studies on plant developmental systems. The general aspects of the problem of plant hormones have been reviewed and discussed by Wardlaw (96) and Nitsch (97). An outstanding contribution in this field has been made by Jacobs (98, 99) whose studies on wound healing in plants show that the concentration, flow, and polarity of flow of auxin determine the pattern of xylem differentiation around the wound.

However, as Weiss (100) and Weiss & Rossetti (101) have pointed out from results of a study of the effects of thyroid grafts on mitotic activity in adjacent hindbrain neurons, it appears that hormones do not create differentials among equipotential tissue units but merely help realize pre-existing latent differentials. In other words, to paraphrase Weiss, we had better not rely too much on the current predilection for diffusible chemical agents.

Gradients and fields: developmental centers.—In his search for some sort of transcellular, "organismic agent" which might serve to unify and control the orderly and proportioned transformations of the developing organism, the student of development has postulated and attempted to demonstrate the existence of embryonic gradients or fields and "organizers." The serious student can hardly deny the existence of some sort of organismic unifying prin-

ciple, but diverse and rather obscure concepts as to its nature and mode of operation have arisen. The need for caution in our thinking along these lines has been emphasized in a recent symposium (102) and by Weiss (100, 103).

Nieuwkoop (104) after summarizing and examining the evidence for the existence of a neural field comes to the conclusion that the neural field is "a spatially-limited and regionally-structured area with gradient-fields of neural differentiation tendencies." There is thus no single gradient field but actually a mosaic of smaller fields. A strikingly similar pattern of organization has been described by Hadorn *et al.* (105) for the larval, genital disc of *Drosophila* which is a mosaic of fields in which each field produces a single element of the genital apparatus. One-half of each field, however, is capable of regulating to form a whole genital element. A somewhat similar mosaic of overlapping fields rather than a single over-all field in the mesoderm of the *Amblystoma* neurula has been demonstrated by Muchmore (106). One of the most interesting examples of the operation of some sort of field control over differentiation has been provided by Nieuwkoop, *et al.* (107). A strip of early gastrula ectoderm was implanted into and perpendicular to the presumptive neural plate area. Such an "appendage" transplant differentiates in a proximo-distal sequence into a neural, mesectodermal, and ectodermal zone. Furthermore, the extent of neural induction in the implant is equivalent to the lateral extension of the neural plate of the host, indicating that in normal development a neural field is evoked in the ectoderm mainly from the median portion of the archenteron roof, which field extends in all directions over distances proportional to its local strength.

Whatever the actual nature of an embryonic field may be, it seems now that we are dealing with a mosaic of overlapping differentiation tendencies and not with an undifferentiated population of equipotential cells. Indeed, the cell population may be quite heterogeneous if one is willing to admit the possibility that the segregative type of differentiation has been going on prior to and during the formation of the various organ-field areas [cf. the studies of Holtzer (217) on the urodele spinal cord]. Each different field or area might contain different numbers of the same cell types as well as different cell types, and this alone might be the basis of its regulative properties.

The progressive segregation in time and space of differentiation tendencies among members of the cell population certainly seems to occur as the developmental centers of the system (such as the shoot apex in plants and the blastopore lip or tail bud of vertebrate embryos) move away from their cellular division products. This phenomenon, which makes possible the elongation of the system, has been studied by Ball (108), among many others. in the case of the shoot apex and by Spratt (109, 110, 111) and Gaertner (112) in the case of the blastopore and tail bud of the chick embryo. It is suggested that stem cells in the developmental center give rise to all of the cells of the axial organs (e.g., notochord, somites, lateral plate, spinal cord, etc.) although some of the members of the cell population may be several genera-

tions removed. Diversity of cell types would vary directly but regulative capacities indirectly with distance away from the center.

At any rate the problem may well be an ecological one [cf. the "molecular ecology" ideas of Weiss (100)]. Nevertheless, we are still faced with the problem of the nature of cell-cell interactions, and this brings us to a consideration of the mechanism of induction.

Mechanism of induction.—This important problem has been recently reviewed by Eakin (113), Brachet (114), and Holtfreter (115). The latter embryologist, in summarizing the present status of the problem, comes to the conclusion that if there are any such substances as individuating "modulators" or inductors (which is unlikely) they do not come from the many inductor substances that have been used but arise *de novo* within the reacting materials. In the case of neural induction, which has been most thoroughly studied, the reaction in the competent ectoderm seems to go beyond the control of the inductor substance which thus acts only as an evocator or initiator of a series of reactions (115). The common denominator of the many neuralizing agents seems to be their ability to cause reversible denaturation of proteins within the reaction system [Brachet (114); Holtfreter (115); Rapkine & Brachet (116)].

Recent studies on the eyecup lens induction reaction have been discussed by Woerdeman (117). The question as to whether or not a diffusible substance (either intra- or extracellular) mediates the interaction between the eyecup and the overlying ectoderm may be raised. The precipitin reaction experiments of Ten Cate & Van Doorenmaalen (118) show that rather specific lens proteins arise during early stages of lens induction in the chick and frog. Does a specific lens inductor substance pass from the eyecup to the prospective lens cells? Does this substance diffuse from the eyecup to the lens area or is cell-cell contact necessary? The recent studies of McKeehan (119), in which cellophane was inserted between the eyecup and overlying ectoderm in the chick embryo, seem to indicate that cell-cell contact is necessary for lens induction. Since the cellophane blocks used were relatively thick, the possibility still remains that an extracellular diffusible substance may be involved. Brachet & deScoeux (120) reported that there was some evidence of induction of neural plate when amphibian ectoderm explants were separated from chorda-mesodern by cellophane with 3.4μ pore size, but no induction when cellophane with much smaller pores (200 mμ) was used. In the large pore cellophane it is possible that cell-cell contact through intercellular bridges could have accounted for the positive results. Further evidence for the necessity of cell-cell contact in induction reactions is found in the failure of hydranth induction in *Cordylophora* to occur through agar or cigarette paper barriers [Moore (121)]. The conclusion then is that cell-cell contact seems to be an important if not requisite condition for induction reactions [cf. Weiss (100); Brachet (114, 120a)]. Nothing, however, is known about the possibility that intracellular, diffusible substances might pass from one cell to another via intercellular cytoplasmic connections.

Further studies on the mechanism of induction which have been carried out by Brachet (114), Shaver & Brachet (122), Fautrez (123), and Kuusi (124), indicate the importance of cellular granules in the reaction. Brachet (114) summarizes the evidence for the role of ribonucleoprotein granules in induction. Ranzi (125) claims that polymerization and depolymerization of fibrillar proteins is a very important aspect of embryonic induction and determination. These studies are very suggestive and their continuation should yield significant results. The importance of nucleoproteins in inductions is indicated by the work of Toivonen & Kuusi (126) and Toivonen (127, 128). Loss or great reduction in inductive capacities of liver or kidney extracts after treatment with proteolytic enzymes would seem to indicate this. The loss of inductive power in coagulated ox muscle protein extracts by air drying [Yamada (129)] indicates the importance of protein structure.

Morphogenetic movements.—The role which the orderly patterns of cell movements play in making possible cellular interactions at the correct time and place is an all important one in the control of development [cf. Holtfreter (115); Bonner (130)]. Morphogenetic movements which are related to the gastrulation process have been recently analyzed in the fish by Trinkaus (131, 132, 133) and Devillers (134), in amphibians by Lewis (135), in the chick by Nabrit (136), and in *Dendraster* by Moore (137). Patterns of morphogenesis and morphogenetic movements in slime molds continue to be studied by Bonner who has recently reviewed his work (130, 138). The role of the diffusible substance, acrasin [Bonner (139, 140); Bonner & Slifkin (141); Pfützner-Eckert (142)], in initiating aggregation of the amoebae and in controlling the proportions of stalk and spore cells during the fruiting process unfortunately still remains somewhat obscure. The role which cellular heterogeneity [Bonner (138); Sussman (143)] may play in the aggregation and culmination processes should not be overlooked.

Attempts to analyze the physiological mechanisms underlying morphogenetic cell movements in slime molds have been made by Allen & Price (144), Loewy (145), Gregg (146), and Hirschberg & Rusch (147). Flickinger (148) has made a similar attempt in his study of pigment cell movements in amphibia. Spratt (149, 150, 151) has studied certain aspects of the physiological and nutritional requirements for morphogenesis in the explanted chick blastoderm. The importance of mechanical substrates in controlling the shape and movement of mesenchyme cells has been shown by Weiss & Garber (152). A similar role of the mechanical substratum in guiding nerve outgrowth has been reported by Weiss (153) and Ferreira-Berrutti (154). The importance of attachment fibers between the blastomeres and the hyaline layer in early cleavage of the sea urchin egg is indicated by studies of Dan and Ono (155, 156). The role of cell deaths in normal vertebrate ontogeny in helping to shape the form of organs has been discussed in a review by Glücksmann (157). Regression of the Müllerian duct in the male chick embryo seems to involve a sort of digestion of the cells which is independent of the

rest of the embryo since it will occur when the duct is isolated *in vitro* [Wolff *et al.* (158)].

External environmental agents.—Modifications of development by means of changes in the external environment and use of various chemicals are almost legion. Most studies to date on the nutritional or *in vitro* cultivation requirements for growth and differentiation of the developmental system reveal information about the metabolic changes which furnish energy for development, but tell us little or nothing about the mechanism of differentiation itself. A few recent studies along these lines are those of Spratt (150, 151), Trinkaus & Drake (159), Harrison (160), Grobstein (161, 162), Howard (163), Berrian & Dornfeld (164), and Wilde (165). The inhibitory effects of vitamin analogues (166, 167) fall into this category. Numerous studies on the effects of oxygen deficiency (168, 169, 170), oxygen pressure (171, 172), x-radiation (173, 174), ultraviolet light (175), carbon monoxide and light (176), β-radiation (177), temperature or thermal shock (178, 179, 180) are mentioned for purposes of reference only.

Studies of the effects of diverse chemicals on embryos are too numerous to discuss but a few are listed below: on oxygen consumption and animalization of sea urchin eggs (181, 182), on developmental patterns in sand dollar eggs (183, 184), on neural histogenesis in the fish embryo (185), on growth and respiration of the amphibian embryo (186 to 189), on micromelia and rumplessness in the chick embryo (190, 191), and on the head and tail of the mammal embryo (192). Interpretation of the results of these diverse studies would at present be very difficult and perhaps misleading.

EXPRESSION OF LATENT POTENTIALITIES

When the developmental system is subjected to adverse but not fatal treatment (surgical methods usually have been used) it attempts with varying degrees of success to maintain its integrity by reorganizing what is left into a semblance of its original form. This may or may not involve growth (net synthesis) to restore the original mass but it undoubtedly involves differential growth (and degrowth) of chemical constituents in the attainment of a balanced whole. The question as to how much the revelation of latent potentialities tells us about the mechanisms by which normal development is controlled remains an open one. Only a few of the many recent studies of regeneration will be cited below.

Weisz (193, 194) has continued his interesting studies on regeneration in the protozoon, *Stentor*, and has summarized them recently (195). The joint role of cytoplasmic granules (kinetosomes) and the macronucleus seems to have been demonstrated. Regeneration in hydroid coelenterates has been studied by Moore (121), Miller (196), and Kemp (197). Moore describes the activities of interstitial cells which participate in induction but do not contribute to the regenerant tissues.

The important role of neoblasts in planarian regeneration has been

demonstrated by Dubois (198, 199). Induction of planarian eye regeneration has been studied by Chow (200), Lender (201, 202), and Wolff & Lender (203). Moment has continued his studies on annelid regeneration and finds additional evidence for his theory of growth limitation by the building up of a critical inhibitory voltage (204, 205).

In amphibian limb regeneration, the important roles of the nerve supply (206), epidermis (207), and hypophyseal hormones (208) have been shown. Studies on the reversal of proximo-distal polarity of the limb (209, 210) confirm the earlier discovery of Butler (211). Suppression of cell division in the regenerating limb by x-rays (212) and by carcinogens (213) may occur without any inhibition of regeneration. Thornton (214) reports that denervated, unamputated limbs regress extensively when injured in contrast to control limbs which recover quickly. Wolff & Wey-Schué (215) have demonstrated the importance of cell migrations during limb regeneration in *Triton*. In his studies on retina regeneration in the salamander, Stone (216) states that the pigment epithelial cells are the only source of origin for the new neural retinal cells.

Studies on regeneration and regulation in the central nervous system of the urodele (217, 218), chick (219), and fish embryos (220) are reported for reference. Among other studies on regulation during early embryonic development those of Colwin & Colwin (221, 222) on *Saccoglossus*, Dollander (223) on the two blastomere stage of *Triton*, Lutz (224) on experimental polyembryony in unincubated duck and chick embryos, and Abercrombie (225) on the primitive streak of the chick embryo are noteworthy.

METABOLISM

The rapidly increasing number and diversity of studies on the chemistry of development warrants a separate and full length review. Consequently, only a very few of the many recent contributions to chemical embryology will be cited here. It should be emphasized that almost all of the studies deal with the chemistry of the cell machinery which furnishes energy for the developmental processes but reveal little or nothing about how the cell structure utilizes this energy for carrying out the work of development: maintenance, growth, cell movement, and cell differentiation.

Chemical embryology of salmonid eggs has been recently reviewed by Hayes (226). Krahl (227) has reviewed the extensive literature (8½ pages of bibliography) on metabolism of sea urchin eggs. Suggestive studies on enzymes (228) and growth promoting factors (229) in sea urchin eggs are being carried on by Gustafson *et al.*

Barth & Jaeger (230, 231, 232), Krugelis (233), and Kutsky (234) have continued their studies on the phosphate transfer system in amphibian embryos. The association of phosphatase activity with cellular behavior during amphibian limb regeneration has been studied by Karczmar & Berg (235). Interesting studies on nucleic acid changes (236, 237, 238) during amphibian egg development are cited for reference.

In a recent conference on "The Chick Embryo in Biological Research" (239), the following topics covering the field of metabolism were reviewed: metabolism of the early embryo (Spratt); metabolic patterns during later embryonic development (Levy); differentiation of enzymes in relation to functional activities of the developing embryo (Moog); appearance of tissue-specific proteins during development (Ebert); physical and chemical changes in the blood stream (Schechtman); and development of muscle (Herrmann). The reader is referred to the extensive bibliographies in this publication.

Citation of all of the recent contributions to developmental physiology has not been attempted, nor has scientific importance been the only basis of selection. It was considered better to limit the review to those fields which seemed most interesting to the reviewer and to discuss these more fully than would have been possible had all the literature been included.

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ELECTRICAL ACTIVITY OF THE BRAIN[1]

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This review covers the period from July 1950 through June 1952. Because of the reduced number of pages allotted as compared to previous reviews, and because of the numerous papers (about 1200) that have appeared, it has become necessary to limit the review to the physiological aspect of the subject and to exclude most publications on purely clinical observations, including activation methods in epilepsy. It is further to be regretted that for the same reasons the review contains no mention of papers on technical advances and on the relation of the EEG[1] to biochemistry, pharmacology, and metabolism of the brain. Fortunately the clinical and technical papers have recently been excellently reviewed by Brazier (30); brain metabolism has been treated by McIlwain (168), and the role of acetylcholine in the central nervous system by Feldberg (91).

Several books on electroencephalography have appeared in the past two years: the two volumes of the second edition of Gibbs' *Atlas of Electroencephalography* (114), containing chapters on methodology and epilepsy; *Electroencephalography in Clinical Practice* by Schwab (226), a book written particularly for the referring physician; *Electroencephalography. A Symposium on its Various Aspects*, by Hill *et al.* (122); and *Diagnostic Electroencephalography* by Strauss, Ostow & Greenstein (241). Brazier's on *The Electrical Activity of the Nervous System* (29) will undoubtedly be appreciated by many students of neurophysiology. The handbook by the same author (28), *Bibliography of Electroencephalography*, which contains over 3000 references to the EEG literature from 1875 to 1948, is indispensable to all workers in the field. Symposia of the Second International Congress of EEG in Paris, 1949, have now become available (92). Two French treatises on epilepsy written by Gastaut (105) and Martin (187) contain much material of interest both to the electroencephalographer and to the clinician.

Normal Spontaneous Activity of the Brain

Alpha rhythm.—The fundamental problem whether rhythmic electrical activity of the cerebral cortex, particularly the alpha rhythm, represents an inherent property of the cortex itself or whether it depends upon subcortical regulating mechanisms still remains a matter of controversy. An outstanding development has been the technique of the isolated cerebral cortex of cats [Burns (44, 45)]. A slab of cortical tissue, isolated from all connections with subcortical structures and neighboring cortical areas (the blood supply being intact), had no power of producing spontaneous electrical activity, syn-

[1] The following abbreviation is used in this chapter: EEG (electroencephalogram)

chronous or asynchronous, in the anesthetized (44) and unanesthetized brain (45). Despite this inactivity the isolated cells were not dead. A single stimulus applied through surface electrodes could produce, as in the intact cortex, a local negative response followed by a positive wave. Moreover, repetitive stimulation produced in the isolated cortex a type of rhythmic after-discharge known to occur in the intact cortex. Evidence was presented demonstrating that these after-discharges are due to impulses circulating in closed self-re-excitating chains of cortical neurones. If a narrow bridge of cortical tissue connected the otherwise isolated piece of cortex with the rest of the brain, spontaneous waves entered across the bridge and excited the isolated cells. Potentials could also be transmitted through afferent paths to a piece of cortex isolated from the surrounding cortex. These experiments suggest that "spontaneous" rhythmic cortical discharges can be maintained only if driven from a source outside the cortex. Very little afferent stimulation of the cortex will provide widespread and complex activity. The spontaneous cortical rhythms were considered ". . . a complex of local responses to incoming stimuli and probably of afterdischarges transmitted across the cortical surface." Burns' experiments support the hypothesis that the alpha rhythm is due to circulation of impulses in closed self-re-excitating chains in the same way as the after-discharges following cortical stimulation.

This study is a challenge to earlier studies of Bremer (32), Kristiansen & Courtois (152), Echlin *et al.* (84) and Tokay (249), who found that the cortex retains its rhythmic electrical activity after isolation and that this activity is due to an inherent rhythmicity of individual neurones. On the other hand, it favors the concept of Dempsey & Morison that most "spontaneous" brain waves, rhythmic and random, are of extracortical origin, the alpha-like 6 to 12 per sec. bursts being the result of thalamic midline and intralaminar stimulation (*vide infra*). The possibility of electrotonic spread of potentials through the cut which severs the corticosubcortical connections should be considered as an explanation for the different results. Eccles (83) has presented a compromise between the concepts of autorhythmicity of cortical cells and of self-re-excitation in closed neuronal chains.

The frequency of the alpha rhythmic activity would be set by two factors, on the one hand the time curve of recovery of the neurones which is a factor inherent in the neurone, and on the other hand the intensity of synaptic bombardment, which is a function of the activity of closed neuronal chains that have no fixed circuits.

From considerations of the excitability changes following neuronal discharges, it may be inferred that at a low level of continuous synaptic bombardment the most probable rhythm of neuronal discharge is at about 10 per sec. Before a reliable assessment of the composition of spontaneous cortical potentials can be made, a more precise study of the electrical responses of individual cortical neurones seems necessary, particularly with intracellular microelectrodes. Walter (256) in the twenty-fourth Maudsley Lecture, has restated the concept that the alpha rhythm is an example of scanning device.

According to Flexner *et al.* (94) rhythmic potentials can first be recorded from the cortex of the fetal guinea pig at the forty-sixth day of gestation, immediately following the period found to be critical for morphological and biochemical changes which are believed to accompany the differentiation of neuroblasts into neurones.

Gastaut (104) has given data on an alpha-type activity in the temporal lobe, which seems to be separate from the occipital alpha. Ostow (209) has written a comprehensive and critical review of the literature concerning variations in the alpha activity with normal psychic functioning. This author maintains that the "kappa waves" described in 1948 by Kennedy *et al.* (145) are not a separate rhythm, but represent a reinforcement of the temporal alpha activity during mental arithmetic and problem-solving activities. Maddocks *et al.* (174) have noted that patients with precentral activity at alpha frequencies, so-called "alphoid" activity, show emotional instability and immaturity and have dominant impressions of color to flashing light, while "nonalphoid" patients have dominant impressions of forms. Palmer & Rock (211) have studied the relationship of high alpha incidence throughout the cortex and personality patterning, and Darrow *et al.* (64) report on modifications of the out-of-phase relationships between precentral and occipital alpha activity in emotionally disturbed children. Stamm (233, 234) concludes that latent times of blocking of the alpha rhythm are indications of centrally determined psychophysiological processes such as "attention to the stimulus." Kreezer & Smith (151) find no statistically significant correlation between alpha frequency and IQ in adults with mental deficiency. In patients with anxiety neurosis Faure (87, 88, 89) has postulated some dysfunction of the alpha-regulating mechanism, possibly of the reticular systems of the thalamus and brain stem. This problem has also been attacked in animal studies (90). Bates (17) and Kibbler & Richter (146) have found a close correlation between the phase of the alpha rhythm and initiation of a voluntary movement, and Contamin & Rémond (59) have reported on the normal EEG of unanesthetized rabbits and on a characteristic change in the EEG immediately before a movement.

Beta rhythm.—Mundy-Castle (201) has studied the beta rhythm in normal adults and has found the incidence and amplitude of this rhythm to be higher in mentally normal seniles than in younger adults. In the younger group a significantly higher incidence of beta activity was found in females than in males, whilst in the senile group a higher incidence was found in Europeans than in Africans. According to Mundy-Castle, these differences are possibly related to cultural influences on the EEG. Beta rhythm in anxiety states has been discussed by Hill (122, Chap. IX). Shinners *et al.* (227) found in a group of 28 children whose EEG records showed distinct high beta rhythm, that the predominant clinical disturbance was that of spasticity involving the extremities. It was suggested that organic brain damage is present when high beta rhythm is observed in children and infants. Apposite to this observation is that of Jasper & Penfield (134) who,

by direct cortical recording in man, noted disappearance of the beta waves of the precentral region during voluntary movements. It was pointed out that this effect is strongly reminiscent of the blockade of alpha activity on directing the attention visually.

Theta rhythm.—Walter [122 (Chap. VII), 256] has further outlined the probable relationship of theta activity to immaturity of central nervous integration processes, to mood and temper. Observations by Mundy-Castle (201) support Walter's findings in respect to theta rhythm and emotional level; its augmentation may parallel increasing unpleasure. There is a decrease of theta incidence with increasing age, and evidence has been presented (201) to indicate that theta activity in seniles represents a different phenomenon from that encountered in young normal adults. Theta activity appears to be relatively prominent in many Africans [Gallais *et al.* (101, 102)].

Spontaneous activity of the cerebellar cortex.—Records obtained by microelectrodes from single units in the cerebellar cortex of cats have revealed two forms of spontaneous electrical activity: (*a*) low voltage 150 to 250 per sec. waves, and (*b*) spike discharges at frequencies ranging from 25 to 150 per sec. [Brookhart *et al.* (41, 42, 43)]. Evidence has been presented (42) indicating that both waves and spikes originate in structures in the Purkinje cells, the granule cell layers of the cerebellar cortex, or both, and that they are the result of operation of functionally different mechanisms. The waves are possibly due to fluctuations of membrane potentials of a nonpropagating nature (42) and have been found to be independent of extracerebellar connections (41), and to appear in young animals simultaneously with the appearance of thymonucleic acid in the Purkinje cell nuclei [Snider & Jacobs (230)]. The spikes are related to an all-or-none depolarization of an active membrane and may be produced either by intrinsic (internuncial or efferent) or extrinsic (afferent) units. These two types of units may be differentiated through the local use of strychnine and through differences in the responses to sensory stimulation (41). The intrinsic units were active in isolated areas of the cerebellar cortex (41). Swank & Brendler (244) have recorded a very fast 1000 to 2000 per sec. activity from the exposed cerebellar cortex in unanesthetized dogs. This activity probably represents the interference of many asynchronously firing cells. In frogs the frequency appears to be considerably lower, 5 to 15 per sec. and 22 to 28 per sec. [Machne & Pupilli (167)].

The Diffuse Thalamic Projection System

Arduini & Terzuolo (10) have studied the cortical and subcortical components in the recruiting responses obtained by stimulation of the diffuse thalamic projection system, to use Starzl & Magoun's term (235). Positive recruited potentials and the characteristic waxing and waning in the amplitude of the response were recorded from the subcortical white matter after ablation of the cerebral cortex. These phenomena may thus occur at subcortical levels, and there is no need of postulating the existence of recruiting phenomena and of fluctuations of excitability primarily localized within the

cerebral cortex, although this has not been disproved. When cortical cells are activated by volleys from the medial thalamic structures impinging upon them, a surface negative recruiting response occurs. This response can be reversed in sign by cocainization of the cortex and during the initial phase of anoxia.

The organization of the diffuse thalamic projection system has been the subject of several studies in the past two years. According to Starzl & Magoun (235), the thalamic origins of this system in the cat include the centromedian, intralaminar, anterior, ventralis anterior, and anterior reticular nuclei. These components form a functionally interconnected unit and appear to project to the cortex in a more localized fashion than hitherto assumed, namely to the associational cortex of the frontal, cingulate, orbital, and suprasylvian portions of the hemisphere avoiding the sensory receiving areas. However, recruiting responses have also been recorded from the latter areas [Jasper *et al.* (133)] and from the olfactory bulb [Arduini & Moruzzi (9)]. A similar cortical distribution of the wave-spike complexes with optimal amplitude over the association areas in patients with petit mal has been demonstrated by Kaada (140), by means of a maximum of 75 closely spaced electrodes covering one hemisphere. Further, it appears that the epileptogenic cortical foci in "petit mal variants" all lie within the cortical zones yielding optimal recruiting responses and optimal 3 per sec. wave and spike discharges in petit mal. Petit mal-like attacks have been induced experimentally, not only from the thalamic midline and intralaminar nuclei, but also from the anterior cingulate area [139 (pp. 223, 242), 161]. According to Lennox & Davis (162) the slow spike and wave formation does not represent simply an immature form of the 3 per sec. wave and spike pattern but rather the confluence of three influences: extreme youth, heredity, and neuropathological change.

Anatomic problems raised in connection with the widespread recruiting response have been further discussed by McLardy (169) and Droogleever-Fortuyn & Stefens (77, 78). The former has emphasized that postulation of a separate nonspecific direct thalamo-cortical projection system is inconsistent with the weight of anatomical evidence. The evidence available favors the concept that the "centromedian complex" of intralaminar nuclei acts as a diffusion and distributing centre within the thalamus, thus permitting widespread activation of the cortex by way of the corticopetal connections of some of the specific projection nuclei. Droogleever-Fortuyn & Stefens (78) have demonstrated direct projections from the intralaminar and midline nuclei to the caudate nucleus. It is of considerable interest therefore that the caudate nucleus has been shown to participate in the recruiting response [Starzl & Magoun (235)]. Kaada (140), summarizing the present state of knowledge of the diffuse thalamic projection system, has drawn attention to the fact that the cerebral structures, cortical and subcortical, from which recruiting responses can be produced or recorded, all appear to yield inhibition of spontaneous motor movements as in petit mal epilepsy, thus further indicating

the functional relationship of these structures. Moreover, all responding areas display the best spontaneous alpha-like 6 to 12 per sec. spindle bursts under barbiturate anesthesia (235), an observation which also supports the view of Dempsey & Morison (73) that the barbiturate bursts and the recruiting potentials have a common mechanism.

Gastaut & Hunter (106), in an extensive animal study of the mechanism of photic activation in petit mal, conclude that idiopathic epilepsy is "a disorder in an otherwise normal person presenting nothing more than an abnormally low threshold of thalamic synapses (or perhaps of all synapses)." The electrical activity of the human thalamus has been recorded in normal (260), stuporous (261), and epileptic (231, 232) persons. Rouvray & Rémond (224) have described a modification of the depth electrode.

The Brain Stem Activating System

Magoun and his collaborators have continued their important studies on the brain stem activating system in cats (176, 177, 236, 237) and a similar system has been described in the monkey (98). High-frequency electrical stimulation of the reticular formation of the brain stem and basal diencephalon desynchronizes the electrical activity of widespread cortical areas, including cortically induced strychnine spikes [Arduini & Lairy-Bounes (8)]. This "arousal" reaction is evoked by stimulation of pathways other than the classic sensory paths. Two alternative routes seem to be available for the corticopetal conduction of the reticular activating influence (236): one involving transmission through the ventromedial part of the thalamus, and a second, extrathalamic path involving direct passage into the internal capsule from the sub- and hypothalamus. This extrathalamic ascending pathway closely parallels that for the "secondary response," described in 1936 by Derbyshire *et al.* (74) as a late cortical wave induced by sciatic stimulation under deep anesthesia. Evoked potential studies have revealed a rich wealth of afferent collaterals with the brain stem activating system of somatic, auditory (40, 237), olfactory (19), splanchnic (98), and vagal (70) origin. These findings indicate that the generalized arousal influences on the EEG of sensory stimulation may be exerted indirectly by collateral excitation of the reticular activating system. Gellhorn & Bernhaut (108) found that the effectiveness to rouse the animal under barbiturate anesthesia increased from optic to nociceptive stimulation with acoustic and proprioceptive stimuli in an intermediary position. Marcus, Gibbs & Gibbs (178) have utilized the arousal response in the EEG during sleep in the diagnosis of deafness in the infant and child.

It seems clear from the extensive studies by Jasper *et al.* (133) that those areas of the diencephalon and midbrain, stimulation of which produces generalized regulatory effects upon the electrical activity of wide areas of cortex, also receive projections from many cortical areas. Similar conclusions have been reached by Bremer & Terzuolo (40).

Conversely, subacute and chronic lesions in the rostral brain stem involv-

ing the activating system in the cat are followed by somnolence and cataleptic states, and a cortical potential pattern of the sleep type [Knott & Ingram (127, 128, 149, 150); Lindsley *et al.* (166); Magoun (177)]. These observations support the hypothesis that this portion of the brain stem normally exerts an alerting effect upon the cortex, which is involved in maintaining resting wakefulness. Disturbance of normal waking EEG rhythms is most clear when the intralaminar group of thalamic nuclei are destroyed, and sleep spindles may be suppressed by such lesions, whereas little change follows destruction of sensory relay nuclei [Knott & Ingram (149, 150)]. The next most effective lesions lie in the anterior thalamic nuclear mass (149). Meyer & Hunter (193) similarly have obtained EEG sleep patterns and akinetic and apathetic states with lesions in the region of the anteromedial thalamus [cf. also Baird *et al.* (15)] and also of the upper end of the mammillothalamic tract. Unilateral and bilateral lesions in the region of the mammillary bodies and inferior portion of the mammillothalamic tract produced symptoms of catalepsy and unresponsiveness, but with minimal changes in the spontaneous EEG. Krueger & Wayne (154) found that normal sleep spindle activity is more impaired in patients who have undergone prefrontal lobotomy [cf. also Lennox & Coolidge (157)] than in topectomized patients.

The caudally directed action of the brain stem reticular system upon levels of motor outflow has been brought into new and interesting light with the recent discovery that this system, by stimulation, may selectively accelerate or inhibit the activity of the small gamma efferent fibers of the ventral root innervating the muscle spindles, thus regulating the rate of discharges in the spindle afferents [Granit & Kaada (116)]. Moruzzi & Magoun's suggestion (200) that blocking of reticular relays within the brain stem may be involved in the production of sleep by general anesthetics has been supported by Schneider *et al.* (225) in electrographic studies on cats. In the light of all these studies it seems to the reviewer quite possible that the muscular hypotonia during anesthesia, and also during natural sleep, is at least partly due to a reduced bombardment of impulses of the gamma efferent neurones by the reticular system, thus reducing the afferent inflow of impulses of muscle spindle afferents and thereby the central excitatory state. An excellent review of the brain stem reticular system has been written by Magoun (175).

EEG and Sleep

Sleep may be produced experimentally either by lesions of the rostral brain stem (see above) or by electrical stimulation of the hypnogenic "center" of Hess. Such stimulation in the cat may also induce reversible EEG patterns similar to normal sleep as recently demonstrated by Hess *et al.* (120) and Monnier (196, 197, 198). The first appearance of the early signs of sleep in subcortical structures, particularly in striatum and thalamus, have been reported by Knott *et al.* (148), who recorded from humans, and by Hodes *et al.* (123), who recorded through implanted electrodes in monkeys. Stimulation of the caudate nucleus in monkeys, man [Heath & Hodes (118)] and

cats [Akert & Andersson (5); Kaada (139, p. 148)] may induce sleep-like reactions. Bremer (34) has reviewed the problem of sleep in the light of recent experimental investigations.

The normal rhythms of spontaneous and barbiturate-induced sleep at different ages have been further studied by the Gibbs (111, 114), Nekhorocheff (203 to 206), Kellaway (143), Passouant (212), and Wyke (264, 265). The EEG in barbiturate poisoning coma has been recorded by Wulff (263) and Cohn *et al.* (58), and in insulin coma by Lafon *et al.* (155), Halle & Ross (117), and Nörgaard (207). Cossa & Martin (61) recorded the most prominent EEG changes in insulin coma from the temporal regions and emphasized the similarities between certain clinical manifestations of temporal lobe epilepsy and insulin coma. Bickford (20, 21, 22, 190) has further developed his electromechanical device for automatic control of anesthesia by the EEG. An adaptation of the servomotor mechanism has been described by Verzeano (253) and applied by Forbes *et al.* (95).

Sleep as a valuable activator in epilepsy has been confirmed again in a number of studies (27, 46, 68, 71, 93, 112, 129, 191, 192, 212, 214, 257). Merlis *et al.* (191, 192) found pentylenetetrazole (Metrazol; pentamethylenetetrazol) more effective than sleep in all clinical groups except for the group with psychomotor epilepsy, whereas Jasper *et al.* (135) found sleep less efficient than pentylenetetrazole activation also in temporal lobe seizures. Delay *et al.* (68) advocate a mixture of chloralose and scopolamine as a hypnotic activator. The Gibbs (113) have encountered a new type of discharge consisting of 6 per sec. and 14 per sec. positive spikes during light sleep (different from the 14 per sec. sleep spindles) in 6 per cent of patients with a clinical history of epileptiform disorder. The abnormal spikes appear to take their origin in the thalamus and hypothalamus and are assumed to represent distorted forms of the normal sleep patterns projected to the cortex. Common clinical correlates are attacks of pain, rage and vegetative symptoms. In support of the subcortical origin of the 6 per sec. and 14 per sec. positive spikes, Stephenson (238) has reported two cases with such abnormalities, in which tumors in the vicinity of the third ventricle were found.

Leroy & Verdeaux (163) suggest that vagotonia is the common factor in activation by sleep and hyperventilation, and Walter (256) wonders whether it is the slow waves in the two conditions that release the epileptic discharge. Titeca & Hamoir (248) and Wayne (257) emphasize the similarity between EEG in sleep and in narcolepsy, and Stoupel (240) stresses the epileptogenic nature of some cases of this disorder.

Temporal and Basal Regions

According to Jasper *et al.* (135), epileptic seizures arising within the temporal and basal regions represent about one-half of all focal cortical seizures. The possible role of these regions in psychomotor seizures and in mental disease have provided a remarkable impetus and a steadily increasing interest for clinical and neurophysiological investigation of these areas, particu-

larly the temporal pole. Thus, during the past two years more than 50 papers dealing with this subject have appeared, most of which, however, are concerned with various clinical aspects such as the etiology, diagnosis, medical and surgical treatment of this type of seizures and therefore unfortunately will have to be excluded from this review. Special attention was paid to the temporal lobe at the annual meeting of the American EEG Society in 1950 [see review by Cobb (56)] and at the International Congress of Otoneuro-ophthalmology at Barcelona (104, 210).

Epileptogenic temporal lesions, especially those involving the tip and inferior surface of the temporal lobe extending into the insula, may present particular difficult problems of electroencephalographic localization. Discharges within these areas may be transmitted widely over temporal and frontal regions of the same hemisphere, or may set up isolated and rhythmic discharges in the contralateral temporal or frontotemporal regions. These heterogenous electrographic and also clinical (psychical, visceral, motor, and sensory) manifestations suggest rich connections with subcortical and other cortical regions. So far traditional anatomical methods have failed to reveal subcortical connections for the temporal pole, and the demonstration of such connections by Marsan, Stoll & Jasper (179, 180, 181, 239) by means of electrophysiological methods is, therefore, an important step forward to a better understanding of the physiological mechanisms involved in temporal lobe epilepsy. Three methods for delineating connections were utilized: strychnine neuronography, evoked potentials, and conduction of electrically induced afterdischarges. Close functional relationships were established between the temporal pole of cats (181, 239) and monkeys (179, 180) and (*a*) the septal-fornix system, (*b*) hypothalamus, (*c*) pulvinar-nucleus lateralis posterior complex of the thalamus, (*d*) basal ganglion system, and (*e*) thalamic reticular system (centrum medianum, reuniens).

These and other electrographic studies (105, 132, 135) would suggest three types of localization in cases of temporal lobe seizures: (*a*) those with unilateral temporal epileptogenic foci which may or may not set up prominent contralateral disturbances, (*b*) those with bitemporal discharges which seem independent, suggesting epileptogenic lesions of both temporal poles, and (*c*) those with projected forms of bilateral anterior temporal discharge arising from the subcortical structures shown to evoke synchronous bilateral temporal pole responses. The latter explanation, if correct, may account for some unsatisfactory results of surgical treatment of temporal lobe epilepsy (132, 180, 216).

Kaada (139), in a thesis problem, has studied the complex visceral, somatomotor, and electrocorticographic effects of electrical stimulation of the temporal pole and the functionally related insular, posterior orbital, limbic, hippocampal, and amygdaloid regions in monkeys and cats. Widespread electrocorticographic effects may be obtained from these regions, particularly over the frontal areas. These findings have been largely confirmed in nonepileptic man by Sloan *et al.* (229). Stimulation of the periamyg-

daloid region (139, pp. 225, 242), hippocampus [Kaada, Andersen & Jansen (141)], fornix and anterior thalamic nuclei [Hunter (126)] in cats has evoked attacks resembling epileptic automatisms in man. It is of particular interest that seizures induced from the periamygdaloid region may start with a generalized sudden depression of all brain waves instead of the usual high-voltage discharges (139), a type of seizures which was first described in 1947 by Jasper & Daly (131) in patients with deep anterior temporal foci. This has been confirmed in patients with automatisms by Hill (121), Mazars (189), Jasper, Pertuisset & Flanigin (135) and Martin & Cossa (188). The response has also been produced in man by stimulation of the uncinate region (135) and in monkeys in which the insular cortex had been treated with alumina cream [Cure & Rassmussen (62)]. Liberson *et al.* (165) have noted impairment of consciousness associated with a moderate slowing of the background activity as a result of stimulation of the uncinate region in man [cf. also Kaada & Jasper (142)].

The high incidence of epileptic seizures arising within the temporal pole (including the amygdaloid and uncinate regions) and from the adjacent insular cortex may be due to (*a*) a relatively low seizure threshold of these areas, as demonstrated experimentally in cats (139) monkeys (139, 158), and man (164, 165), and (*b*) a high susceptibility to traumatization of these areas, caused either by closed head injuries in the postnatal period (105) or by birth injury (16).

The technique of recording from the temporal and basal regions has been improved. MacLean *et al.* (11, 170, 171) and Gottschalk (115) have reported on nasopharyngeal electrodes of a new design, and Arellano & MacLean (11) have applied two tympanic leads in connection with two nasopharyngeal and two ear-lobe leads for registering the electrical activity across a limited area at the base of the brain. Kristiansen & Reyes (153), Jones (136), and Pertuisset & Capedevielle-Arfel (217) have found a sphenoidal needle electrode of value in selected cases in localization studies within the same regions. The latter workers have also introduced a needle into the orbit to obtain records of the electrical activity of the ventral surface of the frontal lobe. The coronal triangulation method of Gastaut (104) is a simple method which appears to be of great value in recording temporal and basal abnormalities. A useful study of the unipolar and bipolar registration techniques has been published by Corriol (60).

Cortical Excitability Changes

Students of cortical physiology have long been aware of the great variability of electrical and motor responses to cortical stimulation, even under seemingly identical experimental conditions. Of primary importance, therefore, is an increased knowledge of the nature and time relations of the various excitability changes, facilitation and depression, of cortical neurones which occur spontaneously or in response to direct cortical or afferent stimulation. A number of papers dealing with these problems has appeared in

the period covered by this review. These excitability changes may conveniently be grouped as follows:

Spontaneous slow periodic variation of brain excitability.—Moruzzi *et al.* (199) have observed a pronounced augmentation of several types of evoked electrocortical activities during spontaneous barbiturate bursts and depression during the interburst period. The alternation was attributed to a periodic waxing and waning of background excitability, of which the burst (and the periodic fluctuations of the alpha waves) may be a manifestation rather than a cause. A similar spontaneous fluctuation of very low frequency (about 6 cycles per minute) in the excitability of the visual system was noted by Chang (53). The phenomenon is probably related to the periodic fluctuations in motor response to uniform cortical stimulation described by Hovland & Dusser de Barenne (124) some years ago. Factors underlying all these fluctuations of brain excitability are thoroughly obscure.

Postexcitatory depression; extinction.—Excitability changes of a more rapid time course in response to a single electric shock applied directly to the cortical surface have been studied by Chang (50). The excitability variations of cortical neurones were found to take a general course (although with a longer duration of the events) similar to that described for spinal motoneurones and peripheral nerves, i.e., the stimulus was followed by a period of refractoriness, a supernormal and a subnormal phase. The postexcitatory (or secondary) depression was considerably enhanced (up to 500 msec.) by local application of strychnine. The secondary depression appears to be related to the prolonged negative local cortical potential which has been recorded in response to a single shock applied to the cortex (48). This can similarly be enhanced by strychnine (49). According to Chang (50), the postexcitatory cortical depression probably denotes the same process as the phenomenon of extinction previously described by Dusser de Barenne & McCulloch (79, 81) as a diminution of electrical and motor responses to test stimulation of the motor cortex following a conditioning brief tetanic stimulation of that focus. Extinction, which is always preceded by facilitation, also appears to be related to the postconvulsive unresponsiveness of the cortex to stimulation and to the decreased electrical activity following more violent seizure discharges [Meyers (194)].

Spreading depression and "suppression."—Serious doubt has been cast upon the existence of specific cortical "suppressor" areas capable, upon stimulation, of producing a long-lasting reduction of electrocortical activity. Critical reviews of the phenomenon of "suppression" have been written by Clarke (55), Sloan & Jasper (228), and Kaada (139, p. 93). Sloan & Jasper identified electrical "suppression" with spreading cortical depression of Leão which is a nonspecific phenomenon in the sense that it is not related to any one specific cortical area. Important is the observation that when a wave of spreading depression, induced from any cortical point, involved area 4 it was accompanied by a reduction of the motor response induced from the same area. Thus, the long-latency "suppression of motor response" to stimulation

of area 4 described by Dusser de Barenne & McCulloch (82) similarly appears to be a manifestation of spreading depression. Short-latency reduction of somatomotor activities such as motor afterdischarges and spontaneous movements, however, appears to be related to specific cortical areas [Kaada (139)]. For these quick responses the term inhibition should be preferred instead of "suppression" (139).

A number of studies have been directed at the nature of spreading depression, the conditions for obtaining this response, the concomitant slow potential changes and convulsive electrical activity (85, 86, 156, 182 to 186, 252, 258, 259). Marshall (182) doubts that spreading cortical depression is a normal physiological phenomenon; it is probably an "intriguing but abnormal reaction which has confused experiments on cortical excitability since the time of Fritsch and Hitzig." The phenomenon can readily be obtained by deterioration as a result of cooling the cortex (185), room air exposure (184), and radical internal dehydration (182).

Periodic, rapid variation of cortical excitability.—Following the refractoriness rendered by a conditioning sensory stimulation, variation of cortical excitability has been studied by Jarcho (130), Chang (47, 50), and Gastaut *et al.* (107). There is cyclic change (facilitation and depression) which coincides in time with the repetitive discharges (at about 100 msec. intervals or more) of the thalamocortical reverberating circuit elicited by afferent stimulation as well as by direct stimulation of the sensory cortex (47, 50). This rhythmic variation lasts for about 1 sec. or more and then fades out. It is an indication of the excitability change of cortical neurones in the sensory cortex rather than of the refractoriness of conducting fibers in the afferent pathway (50). Gastaut *et al.* (107), in an interesting and challenging study, have analyzed this excitability cycle in man and in animals by means of photic conditioning and test stimuli and have considered various drugs from the point of view of their action on various parameters of time and amplitude of the cycle. Thus, barbiturates lengthen the refractory periods (recuperation time) and decrease the amplitude of the response; it is an excellent sedative. On the other hand, its antidote amphetamine considerably decreases the time of recuperation. Pentylenetetrazole (Cardiazol; pentamethylenetetrazol), a powerful convulsant, increases the amplitude of the response to a single or repetitive stimulus, whereas trimethadione decreases these parameters and is a strong anticonvulsant. There also appears to be a correlation between "fast" cycles of excitability and fast spontaneous rhythms in the EEG, and between "slow" cycles and slow rhythms. Attempts were made to explain the electrographic and clinical pictures of petit mal, grand mal, and myoclonic epilepsies on the basis of this excitability cycle.

Physiological Neuronography

Strychninization continues to be a valuable tool in physiological mapping of anatomical pathways within the brain. The method has been successfully used in studies of descending connections from area 6 in monkey

(218), between the temporal pole and various subcortical structures (179, 180, 181, 239), between the motor speech areas of both hemispheres (202), between mesial and basal cortical areas in macaque (219), and between the latter regions and the hippocampus (172, 220). Sugar *et al.* (242, 243) have continued their studies on corticocortical connections of the cortex "buried" in sulci in the monkey.

However, limitations of the method of strychnine neuronography have been reported [Frankenhaeuser (97); Wall & Horwitz (254)]. Contrary to earlier claims, absence of strychnine spikes in a given region does not exclude direct neuronal connections leading to it from a strychninized area. Thus, the following structures have been found to show no evidence of synchronous "firing" in the presence of strychnine: the cerebellar cortex (39, 41, 71), the olfactory bulb, the efferent neurones of the vagus nerve (97), the oculomotor nucleus, the Edinger-Westphal nucleus, all segments of the lateral horn cells of the spinal cord, and the dorsal root ganglia (254). Chang (49) has made interesting observations which give some clue to the understanding of the mechanism underlying the convulsive action of this drug. Contradictory to the original thesis of Dusser de Barenne & McCulloch (80) that strychnine acts on the perikarya and the synaptic endings incrusting them, causing these structures to discharge impulses, it was found that strychnine did not affect the dendritic potential of the cortical neurones. The only effect of strychnine is probably to accelerate the process of impulse initiation of individual neurones so as to increase the efficiency of summation and to increase the chance of synchronization. Wall *et al.* (255) proposed that strychnine acts by affecting mainly presynaptic elements in the same direction as potentiation. No evidence of antidromic synaptic transmission could be found in the presence of strychnine (254). Since the strychnine spikes and the "spontaneous" random spikes in focal epileptogenic lesions are commonly considered to denote the same process within the gray matter, these findings should also be applicable to focal epileptogenic spikes.

Cortical Responses Evoked by Afferent Impulses

The evoked potential technique still proves valuable in studies of the central projections of sensory systems and has recently also been applied to man. Eccles (83) has given an interpretation of the various components of the potentials evoked in the cerebral cortex, comparing them with the more readily analysed responses of spinal motoneurones. There is general agreement that all afferent volleys to the cerebral cortex generate therein an initial surface-positive wave usually followed by a more prolonged negative wave. This may be succeeded by a train of repetitive waves. Two explanations have been offered for the initial positive wave: (*a*) that it is the action potential of impulses propagating up to the afferent terminals in the cerebral cortex; (*b*) that it is set up by the synaptic excitatory action of these impulses on the dendrites of the cortical neurones. According to Eccles, the latter explanation appears to provide the only probable explanation of the positive wave, a view

earlier developed by Renshaw *et al.* (221), Bremer (31), and Chang & Kaada (54). The succeeding surface-negative wave is generally interpreted as being generated subsequently to at least one synaptic relay in the cortex and is attributable to the activity of intracortical neurones. Bremer & Bonnet (38) relate the negative wave in the auditory cortex to corticofugal discharge of large pyramidal cells.

The periodically recurring cortical waves have been variously interpreted. Chang (47, 50) relates them to repetitive discharges of a corticothalamic reverberating circuit, a view put forward some years ago by Dempsey & Morison (72) and Gastaut (103), but opposed by Adrian (3) and Bremer & Bonnet (32, 38). Adrian concludes that the rhythm must be generated in the thalamus and that cortical reverberation is not essential since it persists after destruction of the cortex. Bremer & Bonnet attribute the periodic waves to a transitory intensification of the autorhythmic synchronized activity of subcortical neurones in the afferent path, possibly at an infrathalamic level (38).

Somesthetic system.—Woolsey & Erickson (262) have employed the evoked potential method for the study of somatic afferent representation in the postcentral gyrus of man during operations. With appropriate anesthesia, positive and negative deflections and subsequent repetitive discharges could be recorded from sharply localized points in the hand and foot areas. The method "may prove to be a valuable tool for the neurosurgeon, enabling him to identify the sensory cortex under general anesthesia." The same method has been employed by Reyes *et al.* (222) in the study of subcortical sensory pathways in man. Dawson (65, 66) has succeeded in recording the cortical responses in the somatic sensory region through scalp electrodes in healthy subjects, using a technique of superimposing many records of the cerebral response for detecting the small potentials on the irregular background of spontaneous waves. An improvement of this method has been reported (67). Knighton (147) has studied a thalamic relay nucleus for the second somatic sensory area in the cerebral cortex of the cat.

Autonomic system.—With the evoked potential technique it has been possible to demonstrate the existence of central pathways for afferent impulses from the splanchnic nerves. Three independent studies of this problem have appeared in the past year, all of which are in general agreement. The cortical projection areas lie within the trunk subdivision of the contralateral somatic sensory areas I and II and ipsilateral area II in rabbit, cat, dog, and monkey [Amassian (6); Downman (76)]. These areas, therefore, could well be called somatovisceral sensory areas (7). There is a fast splanchnic afferent projection mediated by the A beta group of fibers both in the periphery and in the spinal cord where it courses through the posterior column (7) and the ipsilateral nucleus gracilis to reach the thalamus by way of the medial lemniscus [Aidar *et al.* (4)]. This fast projection is responsible for the localized primary cortical response and repetitive waves (7). Much slower impulses, which are mediated by the splanchnic A gamma-delta groups and which ascend in the

anterolateral (4, 7) and posterior (7) columns, give rise to a localized second early wave and to the generalized secondary response appearing on stronger stimulation. The latter resemble the secondary response described by Forbes & Morison (96) following sciatic stimulation. Thus, the splanchnic afferent projection system differs in no important respect from the somatic projections as evidenced from the form, type and latency of the evoked potentials.

By evoked potentials Dell & Olson (69, 70) have further been able to outline the central projection of the vagus nerve in cats. Short-latency responses were recorded from the thalamus, the orbital cortex and around the fissura prima of the cerebellum [cf. also Bremer (33)]. Slower conducting projections pass to the centromedian and dorsomedial nuclei of the thalamus, to the medial hypothalamic and preoptic regions and to the amygdala. Similar results have been obtained by MacLean *et al.* (173).

Visual system.—The cortical response to photic stimulation has been extensively studied in connection with the application of repeated flashes for the induction of epileptic seizures [see review by Brazier (30)]. Cobb (57) has made use of the method described by Dawson (65, 66, 67) in man, recording a number of successive superimposed sweeps. Gastaut *et al.* (107) have employed photic conditioning and test stimuli in an analysis of cortical excitability changes (*vide supra*). Chang alone (51, 52, 53) and with Kaada (54) has presented evidence of a triple conducting pathway in the visual system which is thought to serve as separate routes for impulses underlying trichromatic vision (cf. chapter on Vision, this volume). This view has been opposed by Bishop & O'Leary (25) and Bishop & Clare (23, 24), but their objections have been contested (53). Response of the visual cortex to electrical stimulation of the optic nerve in rabbits is evident on the first postnatal day when the central visual pathway is still unmyelinated [Hunt & Goldring (125)]. The cortical light response, on the other hand, does not take place until the seventh day when it coincides in time with commencing myelination in the optic nerve. Thompson *et al.* (246) have carefully mapped the first and second visual areas in the rabbit.

Acoustic system.—Important studies of the spatial arrangement of the responses in the acoustic area of the dog to various tones have appeared [Tunturi (250, 251)]. The presence of electric fields in volume conductors, such as the brain medium, makes it difficult with the ordinary evoked potential method to distinguish the parts of the brain showing only electric fields from those containing afferent fibers. In the acoustic area such a distinction has been made possible by applying strychnine locally to the cortex and stimulating with sound. The appearance of an induced strychnine spike in response to the sound stimulus was taken as evidence of the presence of afferent fibers to the point of application. In the middle ectosylvian auditory area the fibers for each frequency terminate in a strip 5 to 7 mm. in length and no wider than 0.2 mm. disposed transversely across the gyrus. In the anterior-posterior direction, the bands are arranged as a series of parallel strips with spacing of 2 mm. per octave over a frequency range between 250

and 8000 c.p.s., the high frequencies being located in the anterior part of the gyrus and the low frequencies posteriorly. A strip localization of a narrow band of frequencies has also been indicated in an independent study by Henriksen & Merlis (119). Evidence of a spatial analyzing mechanism for frequency in the auditory system has also been obtained from microelectrode recording at the level of the inferior colliculus [Thurlow *et al.* (247)] and of the cochlear nucleus [Galambos & Davis (100); Lennox & Madsen (159)]. Bremer *et al.* (14, 35, 36, 37) have elucidated the functional relationship between the first and second acoustic cortical areas in the cat and further demonstrated (26, 33) the convergence and physiological summation of impulses of different modalities and spatial origins on the cerebellar cortex. The use of auditory stimulation as an activator in epilepsy has been further explored by several authors (12, 13, 63, 192, 208, 213).

A vestibular area in the anterior suprasylvian gyrus in the cat overlaps with the anterior margin of the auditory receiving area [Kempinsky (144)] This may correspond to the recently discovered polysensory projection area, responsive to auditory, vestibular, proprioceptive, and tactile stimulation [Mickle & Ades (195)]. The vestibulocortical projections through the inferior colliculus and the medial geniculate body run parallel with the acoustic fibers [Gernandt (110)].

Gustatory and olfactory systems.—A cortical representation for taste on the orbital surface in cat has been determined by mapping the area electrically responsive to stimulation of the chorda tympani [Patton & Amassian (215)]. Adrian (1, 2) has studied the intrinsic activity of the olfactory bulb during odorous stimulation; Kaada (139) has mapped the cortical, and Berry *et al.* (19) the subcortical distribution of olfactory impulses. From the hippocampus a long-latency potential can be recorded (19), apparently comparable to the long-latency visual, acoustic, and somesthetic responses which can be recorded from the same structure [Lennox *et al.* (160, 223)]. These findings [which confirm previous observations of Gerard *et al.* (109)] open a new and challenging interpretation of the functional significance of the intricate hippocampal system. Like the amygdaloid and temporal polar regions, the hippocampus appears to be disposed to convulsoid activity (137, 138, 139).

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WATER METABOLISM[1]

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The application of new quantitative methods to the study of the distribution of water within the body plays an ever-increasing role in physiologic and clinical research. A review of water metabolism must therefore include not only studies of water balance, but also investigations of the dispersal of water throughout the tissues of the body. The use of isotopes adds to the reviewer's responsibilities, because their application to biologic problems has greatly increased our knowledge regarding the exchanges of both water and electrolytes between different fluid phases. An attempt will be made to group researches which have a similar objective and describe results in the order of their development.

Blood and Plasma Volume

Since the accuracy of estimating blood and plasma volume has steadily improved, smaller alterations in volume are significant. Reeve *et al.* (1), therefore, recognizing that the spleen is a storehouse of blood and that its size is readily altered, studied the concomitant blood volume changes. They estimated simultaneously red cell volume with radioactive phosphorus, $R^{32}P$, and plasma volume with the dye T1824, RT1824, in dogs. The sum of these two determinations was considered the true blood volume, (TBV) or 100 per cent. In normal animals the average ratios were $R^{32}P \times$hematocrit /TBV = 1 and RT1824 $\times$ plasmacrit/TBV = 1. After dilatation of the spleen by pentobarbital sodium anesthesia these ratios were altered to $R^{32}P \times$hematocrit/TBV = 1.07 and RT1824 $\times$ plasmacrit/TBV = 0.96. Removal of the spleen, or its contraction following epinephrine, decreased $R^{32}P \times$hematocrit/TBV to 0.85 to 0.92 and increased RT1824 $\times$ plasmacrit/TBV to 1.07 to 1.10.

Raisz (2) reports some effects of experimental expansion of plasma volume in the dog. The substances which were injected rapidly into the veins were dextran, oxypolygelatin, 4.5 per cent human albumin, and isotonic sodium chloride solution. Each of these substances caused expansion of the plasma volume, using T1824 as an indicator, dextran producing the greatest and isotonic sodium chloride solution the least increase. Glomerular filtration and renal plasma flow were increased and were usually correlated with plasma volume expansion. The renal excretion of water, sodium, and potassium was increased, but the magnitude of the increases did not depend on the rise in plasma volume, the volume increase being as great after infusion of saline solution as after colloid. Some experiments of Walker & Keith (3) with acacia, isotonic sodium chloride, and glucose solutions suggest that, if Raisz

[1] The survey of the literature pertaining to this review was concluded June 1, 1952.

had administered isotonic glucose solution instead of sodium chloride solution, the renal excretion of sodium might not have increased. Welt & Orloff (4) have shown in normal men that the increase in plasma volume following intravenous injection of serum albumin caused no significant changes in the total volume of extracellular fluid. The increase in plasma volume was associated with a reciprocal fall in the volume of interstitial fluid. Interestingly enough this increase in plasma volume correlated with a diuresis when isooncotic and hypooncotic albumin solutions were injected but no diuresis resulted with hyperoncotic solutions.

Rodbard *et al.* (5) revealed in experiments in chicks and rabbits that hypothermia reduces plasma volume as much as 30 per cent, but causes little change in the thiocyanate space. They interpreted these findings as being due to a closing of various vascular beds which lock away some of the circulating blood. Experimental hyperthermia in their hands produced little change in plasma volume.

In a few cases of myocardial insufficiency, Keith, Rowntree & Geraghty (6), in 1915 reported plasma volumes that varied from low to high normal values. In one of these cases, the blood volume was abnormally increased. During the intervening years numerous investigators stressed the importance of hypervolemia in the pathologic physiology of myocardial insufficiency. In a recent study Prentice *et al.* (7) reported blood volume studies in a series of patients who had congestive heart failure. They determined the total red cell volume with the P^{32}-labeled red blood cells and from this value and with the aid of the hematocrit they estimated blood and plasma volumes in 27 patients; 12 of these patients had normal blood and plasma volumes; 15 had either an elevated plasma or blood volume. These authors therefore emphasize the variability of blood and plasma volume during congestive heart failure. They also point out that, with loss of edema fluid, in five of their patients the plasma volume increased as compensation returned. These observations indicate that plasma volume in congestive heart failure is not necessarily controlled directly by rise and fall of the volume of the interstitial space. Nickel *et al.* (8) studied the effect of sodium depletion on body fluids in uremia. Despite a decided temporary decrease in the renal plasma flow and glomerular filtration rate, there was no appreciable alteration in plasma volume, extracellular, or total body water. Ziff & Simson (9) report variable alterations in plasma volume in six patients receiving corticotropin therapy; in one, evidence of circulatory decompensation occurred with a marked increase in plasma volume.

Keys *et al.* (10) revealed in their extensive experimental studies on voluntary starvation in young men that as starvation progressed the plasma volume increased relatively to body weight; the rise in blood volume was not as great; thus confirming the earlier observations of Mollison (11). Keys *et al.* also confirmed the previous observation of Widdowson & McCance (12) that in starvation there was an excess of extracellular fluid. Obviously the relation between plasma volume and extracellular fluid volume must be

variable. However, the evidence of the experiments of Keys *et al.* is that the two variables are fairly closely related in normal young men, and in starvation and subsequent recovery.

Cort (13), in a recent experimental study in dogs, injected intraperitoneally hyperoncotic solutions of 12 per cent albumin or acacia, in physiologic saline. This procedure induced blood volume depletion, which was considered the primary variable and led to decreases in glomerular filtration rate, renal plasma flow, and extraction ratio of *p*-aminohippurate. The associated decrease in chloride and water excretion by the kidneys was considered to be in excess of the effect of a depressed glomerular filtration rate. It is of interest that of these experiments which were terminated at the end of three to four hours with abdominal paracentesis and an intravenous injection of physiologic saline solution, the animal did well; however, if these latter procedures were omitted, approximately one-half of the dogs went into shock and died overnight, thus confirming the findings of previous workers that dehydration may cause serious shock.

Leaf & Mamby (14) have brought further experimental support to Varney's conception of the sensitiveness of the anti-diuretic mechanism of the posterior pituitary to changes of solute concentration of the blood serum. That another factor, a simple expansion of plasma volume, may initiate diuresis has been revealed in some experiments of Strauss *et al.* (15, 16) and of Birchard (17).[2] Expansion of plasma volume and diuresis were induced by the injection or ingestion of saline solutions.

Extracellular Fluid Volume

During the last decade estimation of extracellular fluid space has become a much more frequent experimental procedure than previously. The inaccuracies of the earlier methods have been subjected to continual critical analysis. Deane *et al.* (18), in the last year, have revived the use of sucrose, giving a continuous injection of this inert sugar until equilibrium was established within the body. Estimation of the sucrose space by this method closely approximates that of inulin, 17 per cent of body weight. The sucrose method affords two advantages over previous estimations, early completion, within 180 min., and control of the mixing process. Since Deane *et al.* reported their experiments with sucrose, Cardozo & Edelman (19) have introduced a new method of estimating the volume of distribution of sodium thiosulfate. After a brief single injection and the collection of several blood samples over a short period, thiosulfate gives an average extracellular volume of 16.6 per cent of body weight in healthy male subjects. Walser *et al.* (20, 21) recently employed radioactive sulfate for the estimation of extracellular fluid volume and found in man that equilibrium of sulfate was reached rapidly, in

[2] These authors refer to expansion of extracellular fluid volume. I prefer in this connection to think of the increase in the circulating plasma volume fraction as the important factor.

18 min., and that the extracellular volume by this method amounted to 17 per cent of body weight. Thus, thiosulfate and radiosulfate are added to the group of substances, inulin, sucrose, and mannitol, that appear to measure extracellular space in the normal subject. It is of some interest that early this year, Hiatt & Greene (22) demonstrated in short-time experiments in dogs that 90 per cent of intravenously injected nitrate ion can be recovered in the urine. This finding, together with some earlier studies of Keith *et al.* (23) in man, suggests that the inactive nitrate ion might prove satisfactory for estimating extracellular fluid volume.

The recent experiments of Deane *et al.* (24) in man clearly revealed that chloride is not confined to the extracellular fluid volume as measured by sucrose. Their evidence and that of others indicates that intracellular chloride is variable in amount and very labile. This lability is emphasized in the experiments of Threefoot *et al.* (25), who employed long-life radiochloride, Cl^{36}. Their studies particularly demonstrate time-to-time variations in the rate of exchange of chloride between the serum and other chloride compartments. These alterations could readily lead to error in the calculation of chloride space. Nichols *et al.* (26) have recently endeavored to reconcile the smaller volume of distribution of inulin and thiosulfate with the larger volume obtained from chloride balance studies. They gave to nephrectomized dogs a single injection of inulin and thiosulfate, measured the concentrations directly in the tissues, and compared them with simultaneous electrolyte, water, and collagen content. They found that chloride penetrated connective tissue much more readily and more quickly than inulin and thiosulfate, and suggested that when chloride is corrected for its higher concentration in connective tissue, it is biochemically the best measure of extracellular space. Eggleton (27), in similar experiments in the cat, but after injecting hypertonic sodium chloride solutions, demonstrated that the chloride space was larger than the thiocyanate space, but less than the total body water as measured by the distribution of urea. Mokotoff *et al.* (28) took biopsies of gastrocnemius muscle in seven patients, four noncardiacs and three patients with congestive heart failure, after a continuous infusion of inulin over 30 hr. and compared extracellular volume computed from inulin and chloride space. The chloride space was found to be 18 per cent higher than inulin space. With a correction, as suggested by Nichols *et al.* (26) in dogs, the calculated chloride space was 4 per cent higher than that of inulin. These investigators believe that the true value for extracellular water was not evident from their study. Finkenstaedt *et al.* (29) observed that after a single injection of inulin to anuric patients and bilaterally nephrectomized dogs inulin cannot be used to measure extracellular space because of its failure to equilibrate. The results of Nichols *et al.* (26) in the nephrectomized dog would need to be confirmed in the normal animal with added inulin or sucrose equilibration tests before their conclusions as to the value of chloride estimation of extracellular fluid volume can meet the objections raised by Deane *et al.* (24), by Threefoot *et al.* (25), and by Amberson *et al.* (30).

The therapeutic problems involved in the edema of congestive heart failure have stimulated several recent studies, particularly with regard to the electrolytic concentration and the relative distribution of the edema fluid within the different fluid compartments. A frequent puzzling finding has been a low concentration of sodium and chloride in the serum of these patients, despite a large retention of sodium chloride and water. Leaf & Mamby (31) also observed in these patients that the dilution of sodium and chloride in the serum was associated with oliguria and a hypertonic urine and that if the patient was given extra water no diuresis occurred. They attributed this latter effect to an antidiuretic principle, which they were able to demonstrate in the patients' serum. It appears to act in a distinctly different fashion from the antidiuretic pituitary hormone of Varney.

Squires *et al.* (32) measured the distribution of water within the body of five cardiac patients with extensive edema and hyponatremia. In addition to demonstrating a large increase in extracellular volume, they also observed changes in water and salt metabolism during diuresis and were able to demonstrate both a decrease in extracellular fluid containing large amounts of water, sodium, and chloride, and a decrease in intracellular fluid. Water was lost from and potassium was taken up into the intracellular phase of body fluids. These workers concluded that the intracellular phase shares in the body fluid abnormalities of congestive heart failure and these intracellular abnormalities consist of potassium depletion, increased osmolarity of solutes present, and overhydration. Using these observations as a guide for therapy, Elkinton *et al.* (33) made a similar balanced study in edematous cardiac patients, several of whom were given hypertonic sodium solutions, and a few, potassium salts. Some, but not all, patients responded with a diuresis after the sodium solution. Welt (34) reports a similar experience. The results with potassium were too few to be significant. The authors concluded that while systematic sodium depletion may be present and treated successfully by hypertonic sodium solution, other factors are involved in this syndrome leading to retention of water rather than to a loss of salt. Alteration in intracellular osmolarity may be one of these (35). Only when these factors are understood, will the precise indications for therapy of this syndrome be known. In this connection, the results of the experiments of Eggleton (27) on the cat, with hypertonic sodium chloride solution, may be pertinent. Shifts of water from the intracellular to the extracellular phase were less than if the cells had behaved as simple osmometers containing "ideal" solutions.

Weston *et al.* (36) were able to produce water retention and acute hyponatremia, without sodium loss, by the administration of pitressin tannate to patients in congestive heart failure. Concurrently an increase in edema and reduction in urinary output developed. Within 24 to 96 hr. of discontinuation of the drug, the prepitressin status was restored. Such findings support the theory that fluid retention in cardiac edema may in some cases be due to a relatively greater retention of water than sodium chloride.

Last *et al.* (37) demonstrated that inulin and mannitol did not equilibrate

between plasma and interstitial fluid, in cases of congestive heart failure, even after many hours. They also observed that both inulin and mannitol equilibrate at a faster rate across the peritoneal capillaries in cases of cirrhosis of the liver with ascites than across the peripheral limb capillaries in cases of congestive heart failure. There are, therefore, indications in patients who have an abnormally large extracellular volume that the excess fluid may be unevenly distributed. The findings of Nelson *et al.* (38) and of Welt (34) that hyponatremia occurred after paracentesis in patients who had cirrhosis of the liver and ascites also suggest an unequal distribution of extracellular fluid. Several estimations of extracellular fluid volume in patients with renal edema revealed increased volumes. However, no detailed studies such as were carried out in patients with cardiac edema have as yet been attempted. Of particular interest would be concomitant observations of total, plasma, extracellular, and intracellular fluid volumes. The experiments of Last *et al.* (37) clearly demonstrate that estimations of inulin space (and this would appear to apply to sucrose, mannitol, sulfate, and thiosulfate) in edematous patients by the present methods are not entirely satisfactory measurements of abnormal collections of extracellular fluid. However, up to the present time the attempted measurements of extracellular fluid have given us data of importance. A recent report of a few estimations in edematous patients by the rapid thiosulfate method devised by Cardozo & Edelman (19) appears to reveal greater accuracy.

As mentioned in a previous section, Nickel *et al.* (8) observed the effect of sodium depletion in four patients who had chronic renal insufficiency. Despite appreciable temporary changes in renal function, there was no significant alteration in serum electrolyte concentrations, plasma volume, or extracellular water.

The varied effects of corticotropin and cortisone on water and electrolyte metabolism have added a new chapter to hormone research. With their continued administration for therapeutic purposes, further studies have revealed interesting and sometimes serious water and electrolytic changes. Levitt & Bader (39) made several determinations of extracellular volume (inulin space of distribution) and serum electrolytes in patients receiving a salt-free rice diet and a considerable daily dose of cortisone or corticotropin. Under these conditions, they observed a transient but noticeable increase in isotonic extracellular volume of 20 to 40 per cent. Eliel *et al.* (40) treated a series of patients who had lymphoid tumors with corticotropin or cortisone continuously for several weeks. They observed that, on withdrawal of the hormones, certain serious symptoms sometimes developed. These symptoms were accompanied by distinct losses of sodium chloride in the urine and a fall in the concentration of sodium and chloride in the serum. Extracellular water as measured by radioactive sodium was reduced as was the total body water.

Total Body Water

The measurement of total body water in the living human subject has

become increasingly important in the last few years. The problem was to find by trial and error a suitable substance that would rapidly diffuse and reach equilibrium throughout the total water of the body. Urea was employed by McCance & Widdowson (41), but it has certain practical and theoretical disadvantages. Recently Holman & Lous (42) demonstrated that N-methyl-2-pyridone-5-carboxylamide has a volume of distribution that approximates that of urea. Further studies seem indicated as to its suitability for total water estimations. With the introduction of isotopes into medical research, heavy water in the stable isotope form of deuterium oxide, and the radioactive form of hydrogen, tritium, offered possibilities of determining total body water with greater accuracy. Actual estimations of body water by these two isotopes give comparable values in the normal subject, and the experiments of Prentice *et al.* (43) with tritium and of Schloerb *et al.* (44) with deuterium are in essential agreement. Both groups of workers realized that average values obtained in normal persons are greater in men than in women and may be a small percentage too high in both. The average total body water in men was 60 to 62 per cent and in women 52 per cent of the body weight. In 1949, Soberman *et al.* (45) reported their results with the use of antipyrine in the measurement of total body water. Their original findings, together with those of others carried out later, reveal reproducible values, but the average percentage of body weight with antipyrine is lower than that obtained with the isotopes; that for normal men 56 per cent and for normal women 48 per cent of body weight. Investigators employing either of these isotopes and antipyrine in the same subject, agree that there is experimental evidence that the isotopes may reveal a volume slightly greater than the true volume and antipyrine may reveal a volume slightly less than the true volume. Soberman *et al.* also made comparable estimations of total body water in the same persons by computing the body water from the estimation of the subject's specific gravity and from the dilution of antipyrine. Both methods gave similar values. At this juncture it is of interest to point out that in a series of edematous patients, Hurst *et al.* (46) compared the total body water, before and after removal of the edema fluid, using both deuterium and antipyrine. The actual volumes obtained were greater with the former than with the latter, but the estimated volumes of fluid lost by the patients as computed by both methods were reasonably close; with deuterium the average loss of fluid amounted to 9500 cc., with antipyrine 8600 cc.

Edelman & Moore (47) pointed out that following the rapid intravenous injection of deuterium, a characteristic arterial time-concentration curve is obtained. From its early slope extracellular volume can be computed. This value, obtained by extrapolation of the curve back to zero time, amounted to 15 per cent of the body weight in humans, a figure approaching the 16 to 17 per cent observed with the inulin and sucrose methods. From a later portion of the curve, when deuterium equilibrium is established, total body water can be computed in the usual manner. Although these studies required specially trained investigators and considerable laboratory technique, they

reveal a possibility that further research may simplify and combine estimations of extracellular and total body water. At this point, it is of interest to refer to the combined estimations of plasma volume, extracellular volume, and total body water in normal men by Hardy *et al.* (48). Their results indicate that plasma volume and extracellular volume are more closely related to total body water than with body weight.

It is becoming more and more apparent that methods are needed for estimating total and extracellular fluid volumes in patients who have developed edema. There is uncertainty during the course of a given disease as to the distribution of the excessive fluid between the three body compartments, circulating blood plasma, extracellular and the intracellular fluid spaces. Since in edematous patients there are variables additional to those present in the normal subject, factors such as the diffusion of a given agent and the time necessary for reaching equilibrium in the tissues generally need particular study. Hurst *et al.* (46) have studied some of these factors in 14 cases of cardiac decompensation and a single case of chronic nephritis with edema, using both deuterium and antipyrine. They demonstrated that equilibrium of both substances was greatly delayed and may not be reached even after many hours. The diffusion of antipyrine was slower than that of deuterium. There seems no doubt that in massive cardiac edema, and in the marked ascites associated with cirrhosis of the liver, the total body water may be increased in addition to the augmented extracellular volume. The distribution of the edema fluid in lipoid nephrosis and in chronic glomerulonephritis with edema needs more detailed investigation. Haley & Woodbury (49) have determined the deuterium space during the course of pregnancy. They found it was normal in midpregnancy, but increased during the final two-thirds. In four of five patients, they observed a decrease in total body water during the week following delivery.

With the advent of methods for the quantitative estimation of total and extracellular fluid volumes in the living person, some very interesting analyses of the total amount of water, cellular mass, and fat have been made in normal persons. Rathbun & Pace (50, 51) analyzed chemically the total content of fat, water, and combined nitrogen in guinea pigs. Their results revealed a wide variation in fat content, but a relatively constant chemical composition, including water, of the lean body mass. From their own results and those of others, they noted that in six different species of animals, including the guinea pig and monkey, the mean water content of the lean body mass was 73 per cent of the body weight.

Behnke *et al.* (52) demonstrated that fat men have a significantly lower specific gravity (immersion technique) than do lean men, and that the total body fat can be estimated from the specific gravity of the normal subject. Pace & Rathbun (51) also indicated that from the fat content, the total body water can be calculated. Messinger & Steele (53), as well as Osserman *et al.* (54), compared the specific gravity method and antipyrine method for total body water in normal persons. The results with the two methods were in

approximate agreement. It has thus been shown that total body fat and water can be computed from the specific gravity of the body with considerable accuracy, that there is an inverse relationship of the percentage of body fat and percentage of body water, and that the proportion of water is highly variable unless it is expressed in terms of fat-free tissue (lean body mass). The mean of this latter figure was 71 to 73 per cent, which is in close agreement with the mean of 73 per cent found by Rathbun & Pace in smaller animals.

Berger *et al.* (55) revealed that in four normal subjects varying in weight from 48.7 to 78.8 kg. there was also an inverse relation between total body fat and extracellular fluid volume. The next development was the use by Hollander *et al.* (56) of a simple formula for computing body fat. Their formula was: total body fat = body weight − total body water × 100/73.2. This formula was employed by McCance & Widdowson (41) who emphasized the importance of the inverse relation of body fat to extracellular fluid volume. This relation was particularly striking in the study of Widdowson & McCance (12) of undernourished repatriated German soldiers.

Two further series of experiments in this connection confirm the prediction of McCance & Widdowson (41) that these calculations provide a new and probably a practical approach to many problems in physiology and medicine. Dupertuis *et al.* (57) studied the relation of the specific gravity (immersion technique) to body build in a series of 81 normal men. These investigators demonstrated that the first component of the somatotype of Sheldon *et al.* (58), which is a rating of the round, soft aspect of physique, correlates inversely with body specific gravity. They present an equation which permits the prediction of body specific gravity with a small average deviation from figures obtained from immersion. From the predictive values, the average error for the estimation of body fat was only ± 3.5 per cent fat. In a further series of experiments, Dupertuis *et al.* (59) compare the relation of total body water to body build in the same 81 normal men. Body water was estimated by the antipyrine method. In these experiments there was also a correlation between component 1 of Sheldon's somatotype and percentage of body water as estimated by antipyrine. Again an equation is offered which gives a prediction error of 3 per cent from values given by antipyrine. These investigators emphasize that their 81 subjects were a specially selected group of normal men (naval personnel) and cannot be taken as representing a random selection of the general male population.

From the interrelationships of fat, water, and lean tissue, as evolved from the researches of Rathbun & Pace, Behnke & McCance, and Edelman *et al.* (60, 61) devised further expressions for the estimation of these constituents of the body and applied them to the study of acute disease. Their equations were derived from direct measurements of body water, by deuterium oxide dilution, and of lean tissue, by nitrogen balance studies. They demonstrated in acutely ill patients that utilization of fat reached as much as 170 gm. per day, and the deposit of fat during convalescence usually occurred at a rate of 50 to 75 gm. daily.

Water Excretion by the Kidneys

Several notable contributions to renal physiology and to knowledge of the mode of excretion of water and electrolytes were reported during the last year and are now briefly reviewed. Selkurt's experiments on dogs (62) revealed a direct relation between changes in arterial pressure and excretion of water and sodium. Thompson & Pitts (63) reduced renal arterial pressure of dogs by inflating a balloon in the aorta above the renal artery. Following this procedure, there was a decrease in glomerular filtration and in the excretion of sodium and water. The effect of elevated venous pressure on renal excretion was studied by Stamler *et al.* (64). They observed in their animals a persistent failure of diuresis and natriuresis. Farber *et al.* (65) inserted and subsequently inflated a balloon in the inferior vena cava of volunteer subjects. Thus, venous congestion was induced and there followed a decrease in the excretion of water and salts. Two groups of investigators have studied renal function after producing venous congestion temporarily in the limbs of normal subjects. Chambers *et al.* (66) in their experiments observed a decrease in renal plasma flow, in glomerular filtration, and in the excretion of water and sodium. Judson *et al.* (67) in similar experiments prevented antidiuresis by a large blood transfusion or by mannitol diuresis and concluded that diminution of effective circulating blood volume stimulated the antidiuretic response. Elevation of ureteral pressure in dogs to 20 mm. Hg or higher, as demonstrated by Share (68) and by Selkurt *et al.* (69), caused a decrease in glomerular filtration, and a definite fall in the excretion of water, sodium, and potassium. It is also of interest that Sieker *et al.* (70) demonstrated that a period of breathing at a pressure below ambient pressure may give rise to a considerable water diuresis.

Posture, environmental conditions, and the state of hydration are important factors to be considered in a study of water excretion. Many investigators have recognized the damping effect on renal excretion of water by the assumption of the sitting or erect posture. Accordingly, they have carried out their initial experiments with the subject in the recumbent position. Bader *et al.* (71) report that the diuresis following a change from a warm to a cold atmosphere is similar in many respects to pure water diuresis. The similarity is particularly striking with regard to its inhibition by standing and by injection of pitressin.

The effect of saline solutions, injected intravenously, on urinary flow has been studied recently by several investigators. Strauss *et al.* (15) observed that isotonic expansion of the plasma volume by 0.9 per cent sodium chloride solution caused a water diuresis in the recumbent, but not in the sitting subject. Murphy & Stead (72) report like effects in the recumbent subject after similar intravenous injections of hypotonic sodium chloride solutions. Both groups ascribed the diuretic action in part, at least, to diminished antidiuretic activity of the posterior pituitary body. Strauss *et al.* (16) later demonstrated that plasma volume expansion produced by injections of hypotonic sodium chloride solutions was associated with increased renal excre-

tion of water and sodium when the subject was recumbent, but the urinary changes were absent when the subject was sitting. These observations suggest, therefore, that the locus of diuretic action due to expanded plasma volume is in the cephalad portion of the human body. Strauss *et al.* revealed in these experiments the interesting fact that the increased renal excretion of sodium occurred during the presence of hyponatremia, or when there was a decreased sodium load. Cizek & Huang (73), after producing a persistent state of salt depletion in dogs, observed that water diuresis was equal or greater than in the normal control animal. The diuresis occurred in the presence of hypochloremia, decreased plasma volume, and a normal glomerular filtration rate. They believed that the diuresis was due to a change in function of the renal tubules, which in turn was possibly secondary to altered activity of the adrenal cortex.

Two recent series of experiments, carried out by Adolph *et al.* (74, 77, 78) and by Ladd (79, 80, 81), with regard to water diuresis, are of interest. Adolph & Parmington (74), and Møller-Christensen (75) confirmed the earlier observation of Liling & Gaunt (76), that repetition of water administration to rats led to a prompter excretion of the excess water. Adolph & Northrop (77) studied further this adaptation of rats to excess of body water and noted a faster water but slower chloride excretion; the adaptation disappeared after a rest period of two to three weeks. In previous experiments, Adolph & Northrop (78) had been able to rule out any adaptation to the absorption of water from the gastrointestinal tract. They concluded, therefore, that adaptation to water excess in rats is chiefly in the process of excretion. Ladd (79, 80, 81), in a series of investigations of human subjects, studied the effect of previous ingestion of water on the subsequent diuresis induced by the rapid intravenous injection of 0.9 per cent sodium chloride solution. He found that prehydration with tap water 8 to 13 hr., before the saline infusion, caused (with the injection of saline) a copious water diuresis, which was accompanied by an increased excretion of sodium.[3] In fact, the excretion of water equaled maximal diuresis in nonprehydrated subjects. Ladd concludes that prehydration leaves a trace effect, which materially increases the renal excretion of water and sodium 8 to 13 hr. later, and that this phenomenon of water diuresis as well as natriuresis represents a reduction in reabsorption in the proximal renal tubules. The investigations of Crawford & Ludemann (82) reveal a species difference in the effects of isotonic saline infusion on renal function in the dog and man. In both there is an expansion of plasma volume and increased excretion of water and chloride, but in man, there is no sustained rise in the glomerular filtration rate, which is such a constant feature in the dog. Therefore, in man the increased chloride excretion appears to be due to decreased tubular reabsorption. The results of a few of their experiments are similar to those obtained by Ladd in his prehydrated subjects, and thus emphasize the important part played by hydra-

[3] In these experiments chloride excretion paralleled that of sodium. For the sake of brevity only the data for sodium were presented.

tion of the renal cells in this type of investigation. Welt & Orloff (4) pointed out that a solution containing 4 per cent albumin and 5 per cent glucose could produce a water diuresis up to 15 cc. per min. They interpreted this result as a simple isooncotic expansion of plasma volume suppressing the antidiuretic hormone of the posterior pituitary body. Welt & Nelson (83) also studied maximal water diuresis, 20 cc. per min., in normal subjects. They estimated the positive balance of water necessary for continued maximal diuresis to be 1 per cent of the total body water. A larger positive balance of water did not, in their hands, promote any further increase in the rate of excretion of water. In addition, they observed in some of their subjects that the plasma volume may contract, owing presumably to transfer of electrolytes into the gastrointestinal tract, which produces hyponatremia and consequently movement of water into the intracellular space.

Considerable attention has been given to the subject of oxygen consumption by the kidneys during diuresis. Clark & Barker (84) studied the effect of water diuresis, tubular loading with *p*-aminohippurate, and mannitol diuresis on renal oxygen consumption. Blood for analyses was obtained from the renal vein through an inserted catheter and from the femoral artery in 15 male subjects. Their results revealed no statistically significant change in oxygen consumption between control periods and during the excretion of test substances. They summed up their findings by suggesting that the bulk of energy of the kidneys is expended to maintain a steady state which enables work to be done; and external processes, such as urine formation, could be accomplished with little added energy beyond the basic needs of the organ.

Recently there has been a revival of interest in the diurnal variations in water and electrolyte excretion by the kidneys. Borst & de Vries (85), Stanbury & Thomson (86), and Mills & Stanbury (87, 88, 89) have thoroughly reinvestigated the problem in normal men. The decreased excretion during the night, and increased output on waking in the morning, include corresponding changes in water, sodium, potassium, chloride, and bicarbonate. This diurnal excretory rhythm persisted in the face of a temporary disturbance of sleep rhythm, starvation, water, and salt deprivation, the administration of desoxycorticosterone, pituitrin, and a moderate dose of corticotropin. In several respects, the alkalosis and excretory changes which occur spontaneously after waking from sleep were reproduced by short periods of hyperventilation. These reactions of hyperventilation were confirmed in many respects by Singer *et al.* (90). Stanbury & Thomson conclude that these cyclic changes probably are not produced by hormones of the pituitary or adrenal bodies, but by intrinsic metabolic alterations within the cells of the renal tubules. A second group of investigators, Papper & Rosenbaum (91), demonstrated that differences in sodium chloride intake altered the diurnal rhythm. Rosenbaum *et al.* (92) also studied the effects of large doses of cortisone, 200 to 500 mg. a day, and noted that the excretion of water and electrolytes could be reversed and that the action of cortisone altered their cyclic excretion in some indirect manner and not by direct action on the renal excretory

mechanism. Since cortisone may have pronounced cerebral effects, including disturbances of normal sleep, Rosenbaum *et al.* suggest the possibility of a neurologic action producing these changes in renal excretion. It has long been known that the normal diurnal variations in water excretion can be reversed in renal disease and in congestive heart failure. Goldman's studies in cirrhosis of the liver (93) also reveal, in some of his patients, a reversal of water and electrolyte excretion. Jones *et al.* (94) report in their cases of cirrhosis that the reversal of rhythm is accompanied by a nocturnal increase in glomerular filtration and plasma flow. In patients with nontropical sprue, Wollaeger & Scribner (95) observed a delayed excretion of water during the day but a regular nocturnal diuresis. Their metabolic studies revealed that the large nocturnal volume of urine was due to retention of a considerable volume of water in the small intestine during prolonged digestion and absorption of food; when absorption was finally completed the retained water was excreted, causing nocturnal diuresis.

The mechanism and site of action of certain diuretic substances continues to be a subject of active investigation and debate. Farber *et al.* (96) re-examined the effect of digoxin administered by vein to patients without edema and observed a slight but definite increase in the excretion of water and sodium. They also found that it may initiate a prompt and considerable salt and water diuresis in patients with congestive heart failure. A study of the response of the isolated kidney to aminophylline and mersalyl (Salyrgan), by Kupfer *et al.* (97), revealed that aminophylline reduces vascular resistance, while mersalyl if given into the artery causes partial or complete vascular shutdown; if given by vein mersalyl causes minimal vasoconstriction followed by diuresis. This demonstration of vasoconstrictive action by mercury adds interest to the conclusion of Oliver *et al.* (98) that ischemia may play a role in the production of the renal lesions seen after poisoning by mercury bichloride. The short experiments of Axelrod & Pitts (99) in dogs, and those of several weeks' duration by Hilton (100) in normal persons, emphasize the potentiating effect of ammonium chloride on the diuretic action of organic mercury compounds. Both agree that the potentiation is not due to changes in the acid-base equilibrium. Axelrod & Pitts stress hyperchloremia, and Hilton the possibility of some undefined alteration in the metabolism of the renal tubular cells. The difference in interpretation of results may be due to a different reaction in the dog from man or in the duration of the respective experiments. Axelrod & Pitts (101), in a recent communication, report that in the dog both anoxia and a large dose of corticotropin reduce or abolish the natriuresis and chloruresis induced by mercury.

Three series of experiments in normal subjects were devised recently to elucidate the action of mercury on the kidneys. Two groups, Weston *et al.* (102) and Welt *et al.* (103), produced a steady rate of urine flow by injecting intravenously physiologic saline solution containing pitressin. They then injected mercaptomerin and a water diuresis followed. Capps *et al.* (104), after

obtaining a steady diuresis by the ingestion of water, found that mercuzan (Mercurin) produced no change in some, while in others, it produced an increased diuresis. To a second series of subjects, Pitts gave pitressin during a combined water and mercury diuresis and oliguria followed. The experimental results of the three groups of investigators differ in certain respects. The additional administration of saline solution by vein by Weston *et al.* and by Welt *et al.* during the control periods may have been a factor. Welt *et al.* stress the effect of mercury on the reabsorption of salt in the proximal tubule; on the other hand Capps *et al.* suggest that mercury, by increasing the load of ions, secondarily limits reabsorption of water in the distal tubular segment.

The Action of Pituitary and Adrenal Hormones on Water Metabolism

The antidiuretic hormone of the posterior pituitary continues to stimulate important physiologic research. O'Connor (105), in experiments on the dog, has demonstrated that the normal interphase in polyuria, the sixth to eleventh day, after section of the supraopticohypophysial tracts, is due to the escape of active material from the degenerating pars nervosa of the pituitary into the blood stream. The relative retention of water and sodium after the administration of pitressin has been the subject of several investigations. Holland (106) administered pitressin to 12 subjects, while they were receiving a considerable, measured intake of sodium chloride and water. In spite of definite oliguria, and a gain in weight, sodium excretion remained unchanged. Pitressin, in his opinion, exerted a sodium diuretic action which counterbalanced the sodium retaining mechanism of electrolyte dilution. Murphy & Stead (72) confirmed these results, but also noted an increase in the excretion of potassium. Stead considered that the mechanism by which increased sodium excretion limited the antidiuretic effect of pitressin was most likely due to changes in tubular function. Leaf *et al.* (107) have reported some very interesting alterations in the water metabolism of a patient who had diabetes insipidus and was observed to lose polyuria and polydipsia spontaneously. There was evidence of insufficiency of both the anterior and posterior pituitary functions. The decrease in polyuria seemed to reflect a decreased total solute load requiring excretion. Thyroxine, desoxycorticosterone, cortisone, corticotropin and growth hormone had no effect on the renal concentrating ability or water excretion. Hence these investigators conclude that the alleged diuretic actions are not direct effects but are secondary to their action of increasing metabolism and urinary solute load. Glomerular filtration was 50 per cent of normal and was increased to 75 per cent with corticotropin, but growth hormone failed to elevate the filtration rate.

Injury to the brain has led in certain instances to hyperchloremia and hypernatremia (108, 109, 110). In cases reported by Peters (111), and by Post (112), the electrolyte disturbance was considered to be due to acute

diabetes insipidus and dehydration. Whether this disturbance is possibly due to lesions in the hypothalamic region or in the cerebrum is still to be determined.

Epinephrine is known to affect electrolyte metabolism. Rogoff *et al.* (113) observed a fall in the concentration of potassium in the serum of the dog during intravenous injection of epinephrine at the average rate of physiologic secretion. Jacobson *et al.* (114) observed a similar action in young subjects and also a concomitant decrease in the excretion of potassium; the rate of urine flow decreased in two-thirds and increased in the remaining one-third. Pullman & McClure (115) investigated the action of *l*-norepinephrine and found that it decreased the excretory rate of potassium with little change in urine flow. The experiments of Smythe *et al.* (116) in convalescent patients given epinephrine (USP), *l*-epinephrine and *l*-norepinephrine usually revealed an increased urine flow, but a decreased excretion of potassium and sodium. It seems clearly established, therefore, that the medullary secretion of the adrenal does, under certain conditions, affect the renal excretion of electrolytes and water.

The study of the action of anterior pituitary and adrenal cortical hormones received a great stimulus following the introduction of corticotropin and cortisone to clinical investigation and therapeutics. Gaudino & Levitt (117) demonstrated in dogs that desoxycorticosterone caused large shifts of water between tissue cells and the extracellular fluid space. In contrast, Davis *et al.* (118) observed in their dogs, given cortisone, that it had little effect on extracellular fluid volume, but the urine flow increased 41 to 50 per cent. Rosenbaum *et al.* (119) gave large doses of cortisone, 200 to 500 mg. daily, to men during water diuresis and demonstrated rates of urine flow as great as 34 cc. per min., and increases of 50 to 200 per cent over control values. Clinical studies with both corticotropin and cortisone in patients with edema (120 to 123) clearly indicate that these substances may cause either a retention of water or a diuresis. These contrary actions may occur alternately during treatment in the same patient. Thus, Gaunt & Birnie (124) comment that there are two aspects to the action of adrenal cortical hormones on water metabolism which seem at first glance to be mutually contradictory. Overman (125) also discusses the possible antagonistic action of desoxycorticosterone and cortisone and states that such an hypothesis, though accurate in specific limited conditions, cannot be the basis for a general theory of adrenal-ionic physiology.

Water Balance of Cells and Tissues

The regulation of the content of water within the individual animal cell is of vital importance. Numerous experiments have been devised to elucidate the relation of the water content of the cell to that of its surrounding extracellular fluid. These include the recent metabolic investigations of Robinson (126) and of Mudge (127, 128) on slices of the renal cortex. Robinson's experiments in the rat deal chiefly with the hydration of the renal cell. He

concludes that respiration, as measured by the oxygen uptake, is more important than the osmotic pressure of the surrounding fluid in determining the amount of water in the cell. He suggests that the osmotic pressure of the cell fluid is normally 50 to 100 per cent greater than that of the extracellular fluid. Mudge, in his experiments, using slices of the renal cortex of the rabbit, reveals a similar relation with regard to tissue hydration and oxygen uptake. However, Mudge also found that with constant external osmotic pressure, the osmotic pressure within the cell, estimated as the sum of the cations, K and Na, remained essentially constant despite changes in water content. This finding is of course not in accord with Robinson's suggestion. Differences in interpretation of their experimental results, by Robinson and by Mudge, may however be clarified by a combined new experimental approach and by the use of isotope technique. It is of sufficient interest to point out that Squires *et al.* (32) in studies during the resolution of cardiac edema mentioned previously, conclude that the intracellular phase shares in the body fluid abnormalities of congestive heart failure, and that these intracellular abnormalities consist of potassium depletion, increased osmolarity of solutes present, and overhydration.

Water Exchange Within the Body

Estimations of the dilution of isotopes within the body have led to clearer conceptions of the distribution and exchange of water. Such studies, with the isotopes of water, chloride and sodium, reveal that normally these isotopes attain equilibrium with the extravascular body fluids quickly, a fact which in turn indicates a rapid exchange of ions between the fluid compartments. The actual volume of water and amounts of chloride and sodium passing in and out of the blood stream each minute are large and amount to a high percentage of their total content in the blood plasma. These facts were amplified recently by the investigations of Pinson & Anderson (129) and of Burch *et al.* (130, 131) and by a thorough review of the subject by Pinson (132). During the last year, Fogelman *et al.* (133) applied the deuterium dilution technique to the study of hemorrhagic shock in dogs. They were able to show that in this type of shock the volume of distribution of the isotope was greatly reduced, as also was the to and fro rate of transcapillary movement of body water across the vascular membrane.

This reduction in transcapillary movement of body water offers an explanation of certain phenomena that investigators of hemorrhagic shock pointed out during World War I (134, 135). At that time, they emphasized the importance of a rapid restoration of fluid to the circulation, which sometimes occurred spontaneously, but at a slower rate than in the normal subject. Similar studies with heavy water in dehydration states should be of great interest.

Water Metabolism of Small Desert Rodents

The subject of water metabolism of animals dwelling in desert areas

is an intriguing one. I can warmly recommend the review of the Schmidt-Nielsens (136), in which they discuss the many problems involved. Mention here, however, should be made of some recent observations of these investigators (137, 138). They demonstrated that one of the small burrowing mammals of the desert, the kangaroo rat, will remain in positive water balance when dry barley is given as food and no water is imbibed. The factors which play important roles in conserving water in this mammal are economy in the use of water gained from the oxidation of food, a low rate of evaporation of water from the body, and a high osmotic ceiling in the urine. Study of renal clearances revealed a clearance ratio of urea to inulin greater than unity, which of course, indicates secretion of urea by the renal tubules.

Conclusion

A review such as this one discloses the widespread physiologic effects of water. More accurate measurements of blood volume, extracellular fluid volume, and total body water have given us a clearer insight into some of the physiologic problems involving the circulation, kidneys, nervous system, glands of internal secretion, and the metabolism of fat and lean tissues. Now we envisage a more dynamic picture of the inherent physiology of specific organs and their interrelated functions. There are indications that further application of these and similar methods of investigation can aid in measuring the water content of the individual body cell.

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RESPIRATORY SYSTEM[1]

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Regulation of Respiration

Respiratory centers and nervous regulation.—The localization of the medullary respiratory center and its subdivisions, the inspiratory and expiratory centers, has been studied by Rickenbach & Meessen in rabbits (1) and by Amoroso, Bell & Rosenberg in sheep (2) by electrical stimulation and simultaneous registering of respiration, followed by histological examination. Important new evidence for the assumption that a special chemosensitive respiratory center exists in the medulla besides the expiratory and inspiratory centers, localized electrically, has been furnished by Euler & Söderberg (3) who found that slow action potentials could be elicited from the posterior part of the medulla of the cat during CO_2 breathing. These potentials were independent both of the reflex activity and of the general excitability of the respiratory center, and chloralose was found to act selectively, depressing the chemosensitive bulbar regions without impairing the respiratory reflexes.

Hoff & Breckenridge (4) have supplied new evidence for their view that the medullary respiratory centers possess an inherent periodicity, and that the rhythmic activity, in opposition to the generally accepted view, exists independently of vagal and supramedullary influences. They studied the respiratory patterns in dogs before and after vagotomy in medullary, midpontine, and midcollicular preparations. It appeared from their findings that the centers facilitating the sighing (gasping) type of respiration extend at least from the medulla up into the pons or even higher, and that the sighing normally is inhibited by supracollicular structures as well as from vagal influences. The effect of vagotomy in the supramedullary preparation is to release the sighing type of respiration, which in turn inhibits the eupneic breathing: it is not the simple release of eupneic inspirations previously held in check by the Hering-Breuer reflex. This view is supported by the finding that in the medullary preparation after vagotomy, breathing increases in frequency and retains its eupneic character. The development of "apneustic breathing" after vagotomy in midpontine preparations is assumed to be caused by the "release" of a special inspiratory-facilitating region in the lower part of the pons. In further experiments Breckenridge & Hoff (5) investigated the effect of morphine on the breathing pattern in normal dogs and after transections of the brain stem at different levels. The main result of these experiments was facilitation of the sighing type of breathing both in normal animals and after transections at all levels. The authors as-

[1] This review covers the period from July, 1951 to about May, 1952.

sume this to be due to the release of pontine centers which facilitate sighing and which normally are held in check by cortical and subcortical suppressor mechanisms. The third pattern of respiration, i.e., panting, could be released by morphine also in cases after transection as far down as the midcollicular level.

The concept of an inherent rhythmicity of the respiratory centers, advocated by Hoff & Breckenridge, is confirmed by the transection experiments of Hukuhara *et al.* (6) on vagotomized rabbits, cats, and dogs. These authors observed a transient apneusis after section of the pons but ascribed this effect to tetanic stimulation of respiratory muscles caused by the section, in parallel to the temporary accelerating effect caused by sections also at other levels. While Hoff & Breckenridge were unable to separate anatomically the centers for eupneic and sighing respiration, Hukuhara *et al.* claim to have shown that the eupneic center is located in the lower pons while the sighing (or gasping) center is to be found in the upper part of the medulla. This claim is based upon the finding that the respiration suddenly changes to a purely sighing type after section at the lower limb of the striae acusticae. Their failure to demonstrate eupnea in medullary preparations may, however, be due to too brief an observation, for, as it is clearly seen in the curves of Hoff & Breckenridge, eupnea in the medullary preparation does not appear until after a considerably longer time than the observation times used by Hukuhara *et al.*

Bozler & Burch (7) studied the effect of vagotomy on respiration in closed and open chest experiments on dogs and concluded that pulmonary vagal fibers have an excitatory effect on the inspiration. As the effect of vagal block was independent of the mechanical state of the lungs, it was assumed that the volume receptors initiating the Hering-Breuer reflexes were not involved. Oberholzer (8) has given a review of the respiratory responses to vagal stimulation in rabbits. Lanz (9) investigated on rabbits the influences of the stretch receptors in the pleura on Head's tracheal occlusion reaction, i.e., the elongation of the respiratory phase caused by a sudden occlusion of the trachea. It was concluded that the pleural stretch receptors play an important role in the development of the tracheal occlusion reaction. Further observations on the role of the vagus in respiration studied by tracheal occlusion are furnished by Takagi, Hasegawa & Ishii (10). An initial expansion of the lungs (not the chest) has been shown to be necessary for eliciting the cough reflex (11).

Kaada (12) has made an extensive study on the localization of the cortical areas from which inhibition or acceleration of respiratory movements can be elicited in monkeys, cats, and dogs, as well as in one infant chimpanzee and in eight human patients. Two distinct inhibitory fields were found: (*a*) A "medial-basal inhibitory field," and (*b*) a "temporal-inhibitory field." An acceleration of respiratory movements could be produced by stimulation of part of the motor region. It was demonstrated that the respiratory effects obtained by electrical stimulation of these fields are mediated

directly "down-stream" by cortico-subcortical fibers, and by section of the pyramids it was shown that the response is of extrapyramidal nature. The responses obtained were well-integrated acts and represented almost all characteristics of respiratory movements. The author therefore concluded that the effects are probably due to activation of respiratory centers rather than to a direct activation of the spinal motor neurons. Some of the effects obtained by stimulation of the rhinencephalic structures apparently represented mere olfactory reflexes.

The crossed phrenic phenomenon, i.e., the increased activity after cervical hemisection of the ipsilateral hemidiaphragm following blocking of the contralateral phrenic nerve, has been reinvestigated by Lewis & Brookhart (13) using electromyographic recordings from the two halves of the diaphragm. It was found that the increased activity of the ipsilateral hemidiaphragm was closely related to the activity of the respiratory center. During controlled artificial ventilation, such an increase did not occur. Observations on abnormal innervations of the diaphragm have been reported by Robinson (14) and by Brown & Satinsky (15). The latter authors succeeded in obtaining reinnervation of the denervated diaphragm of the dog by joining visceral efferent vagus fibers to the peripheral stump of the phrenic nerve. The reinnervated half of the diaphragm could maintain adequate breathing even after the opposite half had been denervated.

Grandpierre *et al.* (16) demonstrated anew, on anesthetized dogs and normal humans, that passive movements of the extremities are able to call forth an increase in ventilation without concomitant changes in the arterial blood. The increase in ventilation was assumed to be due to reflexes from the muscles or tendons and disappeared or diminished on section of the sciatic nerve.

Chemical regulation.—Leusen (17) perfused the cerebral ventricles of dogs with isotonic solutions at constant pH but with varying concentrations of CO_2 and $NaHCO_3$ and observed transient changes in pulmonary ventilation parallel to the amount of $CO_2/NaHCO_3$ present in the solution. Cross & Warner (18) and Cross & Oppé (19) studied the effect of high and low oxygen concentrations on the respiration of newborn infants, full term and premature, and concluded from their results that infants have an active carotid body reflex. Lyman & Hastings (20) and Lyman (21), from studies on the pCO_2 of the blood of hibernating hamsters and ground squirrels, and from experiments in which CO_2 was added to the inspired air of the animals, found little evidence for the general assumption of a profound loss of sensitivity of the respiratory center in the hibernating state. The experiments, though, suffer from the drawback that comparison is made with pentobarbital-anesthetized animals and that the blood used was venous blood. Rosenhain & Penrod (22) found that respiration and circulation of hypothermic dogs remained adequate until a short time before death, which may be caused by any of several failures. Observations on altered sensitivity of the respiratory

center caused by drugs (23) and in bulbar poliomyelitis (24) have been reported.

Liljestrand (25) studied the effect of acetylcholine on the respiration of cats during chloralose anesthesia. Intravenous injection of 1 to 10 μg. acetylcholine produced stimulation of respiration which was ascribed to the concomitant fall in blood pressure. With larger doses (0.2 mg.) a stimulation was sometimes observed, but in other cases an inhibition was noted. After denervation of both carotid sinus regions, 0.2 mg. caused a more pronounced reduction of ventilation. The results from experiments with large doses were interpreted as evidence that acethylcholine stimulated the chemoreceptors but inhibited the center. In further experiments it was found that local application of eserine to the carotid bodies enhanced the response to 10 per cent CO_2 and to 10 per cent O_2, whereas local application of atropine diminished or abolished the responses to these stimuli as well as to lobeline. The eserine experiments, though, seem less convincing than the atropine experiments. The author concluded that these results are evidence for the assumption that acetylcholine is the chemical mediator within the carotid body.

Nielsen & Smith (26) studied the effect of CO_2 upon pulmonary ventilation at various degrees of acute hypoxia in two normal subjects with pronounced respiratory response towards low oxygen. The oxygen pressure of the inspired air was adjusted in such a way that the alveolar pO_2 at each degree of hypoxia was maintained at a constant level in spite of the changes which took place in the pulmonary ventilation resulting from the variation of alveolar pCO_2. The stimulus-response curves (steady state values of ventilation and alveolar pCO_2 plotted against one another) showed the following results: (*a*) In acute hypoxia, with a pronounced increase in lung ventilation and a corresponding decrease in alveolar pCO_2, an increase in alveolar pCO_2, produced by CO_2 breathing, had no effect or only a slight effect on pulmonary ventilation until a certain value of alveolar pCO_2 (the threshold value of CO_2) was reached. (*b*) When the alveolar pCO_2 was increased above the threshold value, a given increase in alveolar pCO_2 had an even greater effect on the ventilation than it had in normal conditions (normal alveolar pO_2). (*c*) The threshold value of CO_2 at the various degrees of hypoxia studied, was of about the same magnitude (30 to 33 mm. Hg) as in the normal condition. It was concluded that, in the steady state of pronounced degrees of hypoxia, CO_2 did not contribute, or contributed only to a slight degree to the maintenance of ventilation. The entire ventilation (not only the increase) therefore, was maintained practically by the hypoxic stimulus alone acting on the peripheral chemoreceptors. Further, it was concluded that the CO_2 threshold found was most probably the CO_2 threshold of the respiratory center. The increased respiratory response towards CO_2 found in acute hypoxia, when the alveolar pCO_2 was above the threshold value, very likely was caused by an increase in the sensitivity of the center.

The results from the experiments with acute hypoxia were compared with

some earlier studies on the effect of CO_2 on respiration in prolonged hypoxia (27). In contrast to acute hypoxia, the CO_2 threshold in prolonged hypoxia was found to be lowered to such a degree that alveolar pCO_2 actually was above the CO_2 threshold. This lowering of CO_2 threshold occurred at a time when the arterial blood still was more alkaline than in the normal condition. Further the slope of the stimulus response curves was considerably increased. In prolonged hypoxia, therefore, CO_2 is a regulating factor for respiration, and it is possible that the increase which takes place in ventilation during acclimatization is due to increase in CO_2 sensitivity. Several reasons were pointed out to show that the process of respiratory acclimatization can not be explained, as claimed by some authors (28, 29), simply by the secondary decrease of alkali reserve in the course of returning the pH of the arterial blood to the normal level. It was concluded that during acclimatization the ventilation is increased and, after completion of acclimatization, maintained at the new level under the influence of low oxygen pressure which in some still unknown way may act by causing a gradual increase in the sensitivity of the respiratory system to CO_2 (both a lowering of the threshold and an increase in the slope of the stimulus response curves). It was further stated that this effect of low oxygen pressure, which is important also at relatively low altitudes at which no measurable increase of ventilation occurs during acute exposures, eventually may be strengthened by the secondary compensatory decrease in alkali reserve. Gray (30) has proposed the interesting hypothesis that prolonged acapnia increases and prolonged hypercapnia decreases the CO_2 sensitivity; he suggests that this adaptation hypothesis quite accurately can account for the hyperventilation that accompanies acclimatization to low oxygen pressure. However, the considerably diminished alveolar pCO_2 after acclimatization at relatively low altitudes where no measurable changes in pCO_2 occur during acute exposures can not be explained simply by means of this hypothesis. It seems more probable, as suggested above (26), that the gradual increase in CO_2 sensitivity during the process of acclimatization is governed by the low oxygen pressure. Rahn *et al.* (31) in continuation of earlier studies on acclimatization, used breath holding time on pure oxygen as a measure of the sensitivity of the center to CO_2 and have investigated this factor at 14,200 feet. They confirmed their earlier findings that the breath holding time on air as well as on oxygen was reduced with acclimatization and assumed that the reduction reflected the change in alkali reserve. In other studies from the same laboratory, Stroud (32) has measured the breath holding time at a lowered alkali reserve at sea level (NH_4Cl acidosis). He also found a decrease of breath holding time but in contrast to the high altitude experiments, in which the increase in alveolar pCO_2 from normal rest to breaking point (ΔpCO_2) was greatly decreased, the ΔpCO_2 in these experiments was the same as in the normal condition. The breath holding studies, therefore, seem to support the view that respiratory acclimatization cannot be due simply to the lowering of alkali reserve.

Gray (30) recently has published a monograph in which his Multiple Factor Theory is presented in a more complete form. According to this theory a number of factors, particularly H^+, pCO_2, and pO_2 (measured in arterial blood) exert independent effects on ventilation, and the actual ventilation is represented by the algebraic sum of these. Gray assumes that if the alveolar pCO_2 is reduced to values below the normal threshold, as for instance in metabolic acidosis, its effect becomes not just neutral but definitely inhibitory. Correspondingly, in acute hypoxia where pCO_2 and H^+ may be reduced below threshold values, both are assumed to exert an inhibitory effect so that only a very limited respiratory response can develop because of this powerful opposition. In the calculation of the partial effect of e.g., pO_2 these extrapolated inhibitory effects are added to the total ventilatory response to give the "unopposed partial effect of pO_2." In that way, the partial effect of a pO_2 of 30 mm. Hg was calculated to produce a 700 per cent increase in ventilation, whereas the actual increase amounts to only 65 per cent. The results from the experiments on hypoxia (26) cited above, however, show that when the pCO_2, and consequently the cH, in acute hypoxia are lowered to subthreshold values the ventilation at constant pO_2 remained practially the same as at the threshold. Therefore, the subthreshold values of pCO_2 and cH do not inhibit the ventilation as thought by Gray, and the calculated partial effects must be greatly exaggerated. Gray's theory is in agreement with the earlier proposed CO_2-theory (27) in so far as CO_2 according to both theories exerts a specific effect on respiration apart from its effect as an acid; but, whereas Gray considers other agents which influence respiration as independent stimuli, it was in the CO_2-theory assumed that the other agents studied (metabolic acidosis, prolonged hypoxia and muscular exercise) act by increasing the sensitivity of the center to CO_2. In the conditions just mentioned the CO_2 threshold was found to be lowered. According to Gray, the lowered CO_2 threshold is only an apparent threshold caused by changing the level of one of the other stimuli. If this were the case, the slope of the CO_2-response curves in the range below the normal CO_2 threshold should be expected to be less steep than the normal curves (or nearly horizontal as in the experiments with acute hypoxia). In the experiments with metabolic acidosis and with prolonged hypoxia, in which the alveolar pCO_2 actually was considerably lower than the normal CO_2 threshold, the slope of the CO_2-response curves, however, was respectively just as steep as, or steeper than, the slope of the normal curve. The decrease of the CO_2 threshold in these conditions, consequently, was not an apparent one, as claimed by Gray, but was a real decrease. Whether this decrease in threshold should be termed an increase in sensitivity is a question of terminology.

Muxworthy (33) studied the breath holding time during muscular exercise and found that the alveolar pCO_2 at the breaking point was higher than at rest and suggested from these experiments that the sensitivity of the respiratory system to CO_2 was reduced. Hall (34) found that breathing 11.6 per cent CO_2 at 25,000 feet caused a considerably higher increase in ventilaton

than did the same concentration of CO_2 given in oxygen. It was assumed that this difference was due to the hypoxic stimulus, whereas the potency of this stimulus when breathing ambient air was counteracted by the concomitant hypocapnia. As, however, the alveolar pCO_2 in the pure hypoxic state probably was below threshold, the ventilation found in this condition presumably is a more reliable expression of the effect of the hypoxic stimulus than the above-mentioned difference. Because the inspiratory (and not the alveolar) gases were used for the comparison, the difference can hardly be a quantitative expression of the hypoxic drive.

Åström (35) has studied the combined effects of CO_2 excess and O_2 deficiency on the respiration of dogs under pentobarbital anesthesia. The experiments were performed partly on animals breathing spontaneously, and partly on animals with open chest and artificial respiration so that the composition of the inspired air could be varied independently of the respiratory activity. Both chemoceptively denervated and intact animals were studied. Pulmonary ventilation, thoracic respiratory movements, arterial blood pressure, arterial pH, and O_2 saturation could be recorded simultaneously. It was concluded from the experiments that the effect of CO_2, which is elicited mainly from the center, is dependent upon the oxygen saturation: oxygen lack depresses the activity of the center at all levels of cH (or pCO_2). It was further concluded that the stimulating effects of O_2 lack, which is produced entirely via the chemoreceptors, depends upon the prevailing arterial cH (or pCO_2) so that the effect is decreasing with increasing cH. An explanatory theory was put forward, which assumes the existence of two respiratory centers; viz., a chemocenter which responds to CO_2 (or cH) but is depressed by oxygen lack, and a reflex center which responds to afferent nervous impulses, but in diminishing degree with increasing CO_2 (or cH) [cf. (3)]. The data presented are difficult to evaluate because the test periods used are very short (2 to 3 min.) so that steady state values were not obtained. The conclusion drawn from these experiments on pentobarbitalized animals are in contrast to the findings obtained in experiments on the effect of combined CO_2 excess and O_2 deficiency performed on normal intact humans (26). In the latter experiments the CO_2 response to an increase in arterial pCO_2 was not diminished but increased when the arterial pO_2 was lowered. At a constant low pO_2 the hypoxic response was independent of the arterial pCO_2 at values below the CO_2 threshold. At pCO_2 values above the threshold—as judged from the distance between the stimulus response curves in hypoxia and in normal conditions—it was not diminished but increased with increasing arterial pCO_2.

Alveolar Air

Riley & Cournand (36) have analyzed the factors which influence the partial pressure of oxygen and carbon dioxide of alveolar air and blood from a theoretical point of view by using the O_2—CO_2 diagram of Fenn, Rahn & Otis expanded into a four quadrant system, by means of which it is possible

to visualize simultaneously the partial pressures and concentrations of O_2 and CO_2 in the alveolar air and the alveolar capillary blood. In continuation of this approach, Riley, Cournand & Donald (37) have described a method by means of which it is possible to differentiate between the effects of impaired diffusion and uneven distribution of gas and blood in the lungs on the alveolo-arterial pO_2 gradient. The diffusion effect is characterized by the diffusion constant of the lungs and the distribution effect by the ratios of dead space ventilation to total ventilation and of "venous admixture" to total cardiac output. The main difficulty is the determination of a representative value of the pO_2 of capillary blood leaving the alveoli. This value subdivides the alveolo-arterial pO_2 gradient into an alveolo-capillary gradient, determined by diffusion, and a capillary-arterial gradient determined by distribution. The pO_2 of alveolar capillary blood was estimated by a trial and error method using samples collected at two different levels of oxygenation (about 96 and 82 per cent HbO_2 saturation). It could be assumed at these levels that the mean oxygen diffusion gradient and the percentage "venous admixture" remained constant. This method has been used by Donald *et al.* (38) and Austrian *et al.* (39) in studies of patients with different pulmonary diseases. Ryan & Hickam (40) found that patients with severe anemia had a lower arterial pO_2 and a higher alveolo-arterial pO_2 gradient than normals and pointed out that the existence of a normal or nearly normal venous admixture could account for this effect. Fowler, Cornish & Kety (41) present pulmonary N_2 clearance curves obtained during breathing of oxygen from healthy persons and patients with cardiorespiratory diseases. The results were described and analyzed by means of equations developed under the assumption that an uneven alveolar ventilation is of regional nature.

DuBois *et al.* (42) have registered the CO_2 concentration of expired air during single expirations by means of the rapid infrared CO_2 analyzer of Fowler. They found that the CO_2 concentration after the flushing of the dead space attained a gently rising level, the slope of which remained nearly the same (independent of the depth and duration of the expiration) but increased after muscular exercise and in the initial states of voluntary hyperventilation. From the curves the dead space could be computed. It was found that after breath holding the dead space was considerably reduced owing to diffusion and mixing of alveolar air with dead space air. By rebreathing of mixtures with varying concentrations of CO_2, an approximate value of the mixed venous pCO_2 could be determined. In a patient with advanced emphysema, a pronounced increase in the CO_2 concentration with increasing depth of expiration was found. DuBois, Britt & Fenn (43) have computed the fluctuations of the alveolar CO_2 tension during the respiratory cycle. The CO_2 output from the blood to the lungs was calculated by the Fick principle for each tenth of a second, and the corresponding change in the alveolar CO_2 concentration was found by dividing this amount by the "equivalent lung volume" at that time. The "equivalent lung volume" is a term which,

besides the actual alveolar gas volume, includes an imaginary gas volume determined by the CO_2 storage capacity of the capillary blood flow of the lungs, and of the lung tissue itself, including the contained blood. It was computed from an equation which describes the experimentally determined time relationship of the alveolar pCO_2 during breath holding. It was found that the mean alveolar pCO_2 (arterial pCO_2) for normal rest conditions was practically equal to the midexpiratory alveolar pCO_2 and only slightly higher than the mean pCO_2 in the alveolar fraction of the expired air. Fenn, Rahn & Chadwick (44) have discussed the advantages and disadvantages of hyperventilation at altitude for oxygen transport and concluded that, as long as oxygen saturation is less than about 93 per cent, hyperventilation is beneficial. Hall & Hall (45) studied the composition of air expelled from the lungs of human subjects during rapid decompression and found that not only the CO_2 concentration but also the O_2 concentration was higher in the last part of the expelled air than in the alveolar air before the decompression. The high O_2 concentration was ascribed to a reversal of direction of the oxygen diffusion.

Lung Ventilation and Mechanics of Breathing

Elastic and viscous properties of the lungs.—Nisell (46) studied the effect of CO_2 on the elastic and viscous properties of cat lungs in experiments with two isolated lungs perfused in series. One lung was used to equilibrate the blood with the gas mixtures to be studied and the other, which was ventilated separately with an intermittent inflation pressure of constant value, was used to determine the effect on the tidal air volume. In six out of ten experiments it was found that an increase in CO_2 augmented the tidal air volume. From an analysis of the tidal volume curves it was concluded that this increase was mostly due to a decrease in the pulmonary viscance and to a lesser degree to a decrease in the pulmonary elastance. Wick (47 to 50) studied the influence of CO_2 upon the elastic properties of lungs. On artificially ventilated lungs of dogs with wide open chest, he observed that the total lung volume decreased shortly after death but that ventilation with 3 to 6 per cent CO_2 could restore the lung volume nearly to its original size. Further, it was found that isolated lungs or strips of lung tissue placed in an atmosphere of CO_2 would increase their volume up to 700 per cent. This effect was not caused by the bronchial musculature but was assumed to be due to diminished elastic recoil of the lungs, causing the observed dilatation of the alveoli. The CO_2 effect on the elastic properties of the lung disappeared, when the air in the lung was replaced by saline and it was concluded that the increase in volume resulted from diminished surface tension of the alveoli caused by CO_2.

Dayman (51) registered continuously intrapleural pressure and rate of air flow during single respirations in normal subjects and in emphysematous patients. The theory that the intrathoracic air ways can behave as check valves (i.e., collapse when the pressure in the parenchyme surrounding the

air ways exceeds the pressure in the lumen) was confirmed. The operation of the check valve mechanism was found to depend on the interrelated factors of lung tension, pulmonary pressure, and rate of airflow. Lawton & Joslin (52) have studied the pressure-volume curves of isolated rat lungs.

Elisberg, Goldberg & Snider (53) report that the intraoral pressure during a Valsalva-like maneuver (which is described) was systematically 6 to 7 mm. Hg. higher than the intrapleural pressure, and they concluded that in such conditions the intraoral pressure, therefore, after correction can be used for the calculation of the net blood pressures.

Smooth muscles in the lungs.—Various authors have studied the role of smooth muscles in the lungs. Sturm (54) and Niedner (55) claim to have demonstrated strands of smooth muscle fibers in the parenchyma around the alveoli of the lungs, which reacted to touch of the pleura and to small doses of acetylcholine, and Xalabarder (56) recorded action potentials from the surface of the lung and assumed them to be caused by smooth muscles in the parenchyma distal to the bronchiolar muscles.

The influence of reflexes from the arterial presso- and chemoreceptors on the tone of the bronchial muscles was studied by Daly & Schweitzer (57). The experiments were performed on dogs with an open-chest, negative pressure ventilation technique. Alterations in the tidal air were used as indicators for the changes in the bronchomotor tone. From their experiments they concluded that bronchomotor tone is at least partly maintained by reflexes arising in the pressoreceptors of the carotid sinus and aortic arch. Other authors have studied the effect of *Veratrum* derivatives on the bronchiolar muscles (58) and of specific antigens on strips of bronchiolar muscles from human asthmatic lungs (59). A survey of the function of the pulmonary musculature has been given by Stutz (60). Wyss *et al.* (61, 62) conclude, from measurements of the air resistance in the respiratory tract in normals and patients, that the increased resistance in asthmatics plays only a minor role in the dyspnea. The dyspnea noticed during expiration is presumed to be caused by increased tone of the inspiratory muscles brought about by reflexes from the somewhat contracted bronchi.

Lung ventilation and lung volumes.—Using a body plethysmograph, Cross & Warner (18) and Cross & Oppé (63) have mesured the pulmonary minute volume, respiration frequency, and tidal air of newborn, full term and premature infants. A series of data on lung volumes, resting ventilation per minute, maximal voluntary ventilation, duration of breath holding, etc., in 541 children and adolescents at the age from 4 to 20 years was presented by Piechaud *et al.* (64). The results obtained by these authors on vital capacity per kilogram body weight were in all age groups considerably smaller than those found in Swedish youths by Åstrand (65). This author has made an extensive study of the physical working capacity of 113 male and 112 female subjects aged 4 to 33 years (males) and 4 to 25 years (females). In his data are included determinations of lung volume and its subdivisions, and of lung ventilation during submaximal and maximal work. Graphs are

presented which show the relation between vital capacity, lung ventilation at maximal work, etc., and age, height, surface area, and body weight. Morse *et al.* (66) have measured lung volume in 124 boys aged 10 to 17 years. It was found that height was the best single standard of reference. Greifenstein *et al.* (67) studied various pulmonary functions in healthy men and women at ages 50 to 77 years; they compared the results with those from healthy young adults and found that the most important changes were a reduction in vital capacity, an increase in residual capacity and reserve air, as well as a less even intrapulmonary mixing of inspired gas. Despite these changes the subjects maintained normal arterial oxygen saturation, pCO_2 and pH.

Cara & Kohler (68) have estimated the residual capacity from the linear relationship found between maximum breath holding time and filling of the lungs. Muxworthy (69), however, has shown that this extrapolating method gives quite unreliable results. Verzár (70) registered the thorax circumference in a low pressure chamber at a simulated altitude of 4600 m. and found an increased expiratory circumference of the thorax. This finding is discussed in relation to observed lung volume changes in the Andes and was considered a confirmation of his theory of a "third form of respiration regulation." Rahn & Hammond (71) measured the vital capacity during acute and chronic exposure to hypoxia. They found that the decrease in vital capacity was only half as small as that found by other authors and that the decrease was only transitory. The possible effects of engorgement of pulmonary vessels, increased tonus of inspiratory muscles, decreased force of respiratory muscles, and abdominal distension are discussed. Bahnson (72) and Fowler, Guillet & Rahn (73) investigated the effects of possitive and negative pulmonary pressures upon the vital capacity and found that positive pressure increased, and negative pressure decreased, the vital capacity, presumably because of shifts of blood from and to the chest. Sheldon & Otis (74) have studied the effect of positive pressure breathing on the pneumotachogram. McCutcheon (75) studied the respiration in horse and rat and found an increase in tracheal pressure of 18 mm. Hg during expiration caused by a temporary closure of the glottis in the horse; they claimed to have demonstrated in rats an increase of the intrapulmonary pressure of 20 to 40 mm. Hg in connection with a "complementary breathing cycle" (gasps) occurring at a rate of 23 per hour. The author offers the amazing hypothesis that these pressure changes should be an expression of a special regulation of the diffusion of gases in the lungs. Further respiratory data are presented by Georg (76). Lukas & Plum (77) have studied the vital capacity, residual volume, and maximal breathing capacity in patients convalescing from acute poliomyelitis with respiratory paralysis.

Upper respiratory tract.—The nutritional blood supply to the bronchi was studied by Ellis, Grindlay & Edwards (78, 79). They found, in experiments on dogs, that the bronchial arteries are necessary for the nutrition of only the greater bronchi near the hilum, whereas the finer bronchi and the pulmonary

tissues are supplied mainly from the pulmonary artery. The distal parts of bronchial arteries are supposed to be vestigial in postnatal life. Shedd, Alley & Lindskog (80) found indications for functional connections between the vessels of the different pulmonary lobes in dogs.

Taplin *et al.* (81) studied the distribution of P^{32}-marked *Bacillus subtilis* spores after 30 min. of inhalation and after intravenous injection. The dispersion of coal particles in the lungs of miners was discussed by Policard (82), and Davies (83) has studied the relation between particle size in dust and lung diseases. The structure of the tracheal cilia has been studied by means of the electron microscope by Engstrøm (84). Hilding (85) found that ciliary movements could produce a negative pressure in the hen's trachea when it was occluded by a mass of mucus. Proetz (86) investigated in a series of experiments, partly on anatomical preparations, the pathway of air currents in the upper respiratory tract and Stoksted (87) studied the resistance to air flow of the two halves of the nose and concluded that cyclic changes occurred as a result of alternating swelling of the mucous membrane. Ingelstedt & Ivstam (88) studied the tolerance of the mucous membranes of the nose to dry air. Miller, Proud & Berhle (89) found that, of 154 newborn infants, only about one-fourth had a cough reflex during the first five days. In infants over one month, 90 per cent had the cough reflex. It is assumed from parallels to other vagal respiratory reflexes that this is caused by a lack of sensory stimulation (i.e., no vagal connections from pharynx to the center). McCutchan & Taylor (90) investigated the heat exchange in the air ways and concluded that warming of the tracheobronchial system was not a limiting factor in man's susceptibility to extreme heat.

Pulmonary Circulation

Westcott *et al.* (91) and Doyle *et al.* (92) have studied the influence of breathing low oxygen (13 and 10 per cent O_2, respectively) on the human pulmonary circulation and found that the pulmonary arterial pressure increased considerably, whereas the pulmonary "capillary" pressure remained unchanged. There was no increase, or only a slight increase, in the cardiac output, and Doyle *et al.* further found that the pulmonary blood volume was not altered. From these observations it was concluded that the increase in pulmonary arterial pressure was due to an increased pulmonary arteriolar resistance. Fowler *et al.* (93) found that the correlation in humans between pulmonary arteriolar resistance and pulmonary arterial systolic and mean pressure was just as high or higher than between arteriolar resistance and diastolic pressure. Atwell *et al.* (94) showed on dogs that, when one lung was rebreathing through a bronchospirometric catheter while the other lung continued to breathe air, a marked shift of blood flow from the rebreathing lung toward the air breathing lung could occur.

In isolated, perfused cat lungs, Duke (95) found that inhalation of low O_2 or high CO_2 mixtures produced pulmonary vasoconstriction as evidenced by an increased pulmonary arterial pressure. Bean *et al.* (96), working with

isolated ventilated or quiescent dog lungs perfused at constant pressure, observed that perfusion with blood high in CO_2 caused a decrease in outflow and an increase in lung volume; similar changes were obtained by addition of acetylcholine. It was suggested that these results might indicate a constriction on the venous side with a concomitant active or passive dilatation on the arterial side of the pulmonary capillary system. In corresponding experiments on isolated ventilated cat lungs perfused with a constant rate of blood flow, Nisell (97) found that the pulmonary arterial pressure decreased when the CO_2 content of the perfused blood was increased or its O_2 content decreased. It was concluded that high CO_2 or low O_2 dilate the pulmonary arteries or arterioles when these stimuli reach the pulmonary vessels via the blood stream. The constriction of pulmonary vessels generally found during inhalation of high CO_2 (or low O_2) was assumed to occur in the veins or the venules. This assumption was confirmed in continued experiments (98) in which it was found that inhalation of high CO_2 or low O_2 increased the pulmonary arterial pressure and also increased the blood volume of the isolated perfused cat lung. As mentioned above, Bean *et al.* arrived at the same conclusion (constriction of the venules at high CO_2) in experiments in which the CO_2 reached the blood via the blood stream. It must be emphasized that the results from the experiments on isolated lungs cannot be applicable to the whole organism, as the experiments of Westcott *et al.* (91) and Doyle *et al.* (92) clearly showed that the pulmonary vasoconstriction, which takes place by inhalation of low O_2, occurs on the arterial side.

Smith & Coxe (99) found on isolated pulmonary vessels of man and different animals that epinephrine, acetylcholine, and histamine caused vasoconstriction, but that anoxia had no effect. Edwards (100) reported that inflation of a single lobe of lung in the dog increased the pulmonary vascular resistance. Epinephrine had the same effect. Pearce & Whitteridge (101) found a direct relationship between the activity of pulmonary vascular fibers and the pulmonary arterial pulse pressure. The effect of increased interbronchial pressure on the lung capillaries was studied by Schumann (102), and Hamilton (103) has given a discussion of the physiology of the pulmonary circulation.

Artificial Respiration

In continuation of earlier studies on the efficacy of different manual methods of artificial respiration, Sadove *et al.* (104) and Gordon *et al.* (105) have measured the ventilation on anesthetized, curarized volunteers. The results showed, in agreement with earlier experiments on nonrigid corpses, that the "push-pull" methods (Silvester method, Holger Nielsen method, and Emerson-Ivy method) gave about two times as large tidal airs as the Schafer prone-pressure method. Pneumotachograms showed that the induced inspiration and expiration were accomplished after approximately 1.5 sec., and this led to the conclusion that a rhythm of 10 to 12 complete cycles per minute should be optimal. Enghoff *et al.* (106) using the same procedure on female

volunteers, and Karpovich *et al.* (107), who measured the increase in inspiration and expiration which occurs when the artificial respiratory movements were superimposed on normal spontaneous breathing, came to similar results, and the former showed further that, when using the Eve rocking method, the angle of rocking should be over $\pm 30°$ in order to produce adequate ventilation. On patients who were apneic because of intracerebral hemorrhage or other pathological conditions, Whittenberger *et al.* (108) and Nims *et al.* (109) likewise found the Schafer method inferior to the push pull methods. It is interesting to note that the results obtained on the normal, anesthetized, curarized subjects generally show a considerably greater tidal air than those from the above-mentioned apneic patients or from corpses. A possible explanation for this discrepancy may be sought in the experiments of Culver & Rahn (110), who found that pressure applied to the chest of apneic, anesthetized dogs could stimulate the respiration via vagal reflexes. The effects of the different manual methods and of the Eve method on the circulation were tested by Gordon *et al.* (111) on anesthetized, curarized volunteers, by means of heart catheterization. It was found that the Holger Nielsen method, the Emerson-Ivy methods, and the Eve method could maintain adequate oxygenation of arterial blood, whereas the Schafer method of in three out of nine cases was unable to do so, possibly because of an uneven alveolar ventilation.

Details in the air-flow patterns and in pressure-volume relations during artificial respiration were included in the paper of Whittenberger *et al.* (108)' and Nims *et al.* (109) have studied the effect of various modifications of the Holger Nielsen method; the original method seems to be as good as any modification.

The amount of energy spent on performing artificial respiration was studied by Gordon *et al.* (112) and by Karpovich & Hale (113) on male and female operators. Both teams further agreed in rating the Holger Nielsen method the easiest to learn of the push-pull methods (114, 115). Specht & Brubach (116) concluded from N_2-uptake curves after previous N_2 elimination that a larger active lung surface is involved when using the Emerson-Ivy method than when using the Schafer method.

Sarnoff, Sarnoff & Whittenberger (117) have summarized the literature on electrophrenic respiration, i.e., respiration produced by direct electrical stimulation of the phrenic nerve. Automatic devices for producing "assisted respiration" during anesthesia in intrathoracic surgery and for use on newborn hypopneic infants were described by Maloney, Derrick & Whittenberger (118) and Donald & Young (119), respectively. Plum & Whedon (120) described a rocking bed and its ventilatory effect in cases of poliomyelitis with respiratory arrest, and Merlis & Degelman (121), developed an improved respirator for animal experiments. Maloney *et al.* (122) concluded from experiments on dogs, that positive pressure breathing may impair the circulation if the peripheral venous pressure cannot be increased corresponding to the increased intrathoracic pressure, e.g., because of hemorrhage,

sympathetic inhibition, or curarization. Frank *et al.* (123) pointed out the dangers for the circulation of continuous inflation of the lungs.

Miscellaneous

Hypoxia and hypercapnia.—A number of articles deal with the effect of low O_2 pressure on man's work capacity (124), hematopoiesis (125, 126), pulmonary circulation time (127), and with the general physiological and clinical aspects of hypoxemia and its treatment with oxygen (128 to 134). The effects of hypoxia or hypoxemia on different organs or physiological functions have been studied, mostly in animal experiments (135 to 143). Hypercapnia was found to inhibit the corneal reflex at 5 per cent CO_2 in the inspired air, while at 30 to 70 per cent most reflexes ceased (144). In rats, dying from hypoxia, it was found that high percentages of CO_2 inhibited the mobilization of the heart's glycogen stores (145). The dangers of the combined hypoxia and hypercapnia often found in patients suffering from respiratory diseases or during anesthesia have been pointed out and discussed by several authors (146, 147, 148) and it has been emphasized that proper oxygenation cannot substitute for adequate ventilation of the lungs. Kirstein (149) has written a monograph on the effects of hypoxia and hypercapnia on the spinal reflexes. Both conditions seem to diminish the reflex activity of mono- and polysynaptic spinal reflexes. The effects of high CO_2 and low O_2 percentages on electrically induced convulsions in rabbits were studied by Dahlberg-Parrow (150) and Belfrage (151).

Pharmacology.—The effect of drugs given to the mother during labor, on the respiratory function of the fetus has been studied in rabbits (152). Hutcheon & McCullough (153) investigated the effect of octylamines on the respiration, and Hald *et al.* (154) gave an account of an antagonistic effect of alcohol and acetaldehyde on the respiration of rabbits. Dawes *et al.* (155) studied the effect of veratridine and some amidines on the pulmonary reflexes. Li *et al.* (156) found that the respiratory muscles were as susceptible to curare as other skeletal muscles with the possible exception of the diaphragm.

Pulmonary edema.—Cameron & Sheikh (157) and Sarnoff & Kaufman (158) used ammonium salts, and Richter (159) α-naphthylthiourea for experimental production of pulmonary edema. The latter studied further the physiology and cytology of pulmonary edema during its different stages and recommended this technique for use in tests of different treatments of lung edema.

Reviews, books etc.—The problem of intrapulmonary distribution of inspired gas has been fully reviewed by Fowler (160) who also gives an extensive bibliography. A review of the literature in English on cardiorespiratory failure covering the period from 1925 to 1951 has been given by Becker (161). Dyspnea has been discussed in a symposium at the Mayo Clinic (162), and Slome (163) has lectured on the nervous regulation of respiration. Vandam (164) has given a review of the functional anatomy of the lung.

Fenn, Otis & Rahn (165) have collected and issued articles on the physiology of respiration from the University of Rochester. A number of these papers, not published earlier, are reviewed in the foregoing under the proper headings. A book on decompression sickness has been issued by the National Research Council (166).

Methods.—Lorentzen & Brinch-Johnsen (167) have described a method for quantitative gas determinations with the Scholander-Roughton syringes. Erikson, Scholander & Irving (168) have further developed the "gas-layering apparatus" of Scholander into a volumetric recording respiration apparatus, which in continuous tracing shows tidal air, respiratory frequency, difference between O_2-uptake and CO_2-output, CO_2-output in 2-min. periods, and ventilation volume. Behrmann & Hartmann (169) used the Beckmann O_2-analyzer also for rapid determination of CO_2, and DuBois & Ross (170) used the cathode ray oscillograph for recordings of pressure-volume curves of chest and lungs, alterations of tone of respiratory muscles, and pressure-flow curves. The nitrogen meter of Lilly is recommended for respiratory function tests by Lundin (171). Various pieces of equipment for high altitude aviation are reported (172, 173). Hirdes (174) described the technique of bronchospirometry and Flanagan (175) the technique of bronchoscopy. Enghoff, Holmdahl & Risholm (176) have demonstrated that diffusion respiration in anesthetized, curarized man can be tolerated for up to 7 min. The use of isolated lungs as oxygenators in dog experiments has been described by Potts *et al.* (177) and by Gerst *et al.* (178).

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THE DIGESTIVE SYSTEM[1,2]

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During the past year gastric secretion was the foremost theme of research in the field of the digestive system. More than one third of the papers published on experimental gastroenterology were concerned directly with the secretion of gastric juice. Seemingly, neglected topics were digestive and excretory functions, secretion of the small and large bowel, and mechanisms of appetite, hunger, and thirst.

Taste, Appetite and Caloric Intake

In two attempts, using accurate electrical stimulators, Jones & Jones (1) were unable to elicit a fluctuating or pulsating sour sensation from the tongue. In their tests, sour taste was fused at all frequencies at which it was detectable so that it was impossible to obtain fusion frequencies as reported many years ago by Allen & Weinberg. Further work is needed.

Some clinical impressions are accumulating which suggest that substances from the adrenal cortex may affect appetite. In tests done by Quimby (2), however, supplemental injections of adrenal cortical extract had no effect on the appetite of chronically starved rats when they were refed an adequate diet. Injections of liver extract during recovery also had no effect, while injections of vitamin B_1 and B complex stimulated appetite, and injections of growth hormone inhibited it. In dogs, Share, Martyniuk & Grossman (3) uncovered two inhibitory mechanisms influencing intake of food. The first, initiated by gastric distention, was illustrated by the reduced consumption of food which occurred when bulky inert material or a large water-filled balloon was placed in the stomach just prior to feeding. The second, an extragastric digestive factor, was indicated when the placing of more than 33 per cent of the customary daily caloric intake in the stomach 20 hr. prior to feeding time, reduced the intake of food even though the stomach was empty when the food was eaten. Bulk in the intestine was not the cause because similar use of inert material had no such effect.

Secretion

Salivary Secretion.—From experiments by Sand (4), during which blood and salivary concentrations of bicarbonate were determined in human beings

[1] It was originally intended that this review should cover the period July 1, 1951, to the end of June, 1952, and although the bibliography was not closed until mid July, the June, 1952, number of many journals, particularly those from foreign sources, had not been received. No references have been made to abstracts of papers presented at meetings.

[2] The following abbreviation is used in this chapter: ACTH (corticotropin).

during acidosis and in rabbits given C^{14}-labeled bicarbonate or lactate, the conclusion was reached that at least part of the bicarbonate in saliva is formed in the cells of the salivary gland during the secretory process.

Beerstecher & Altgelt (5) have demonstrated the presence of apoerythein (intrinsic factor of pernicious anemia) in saliva by the assay method of bacterial growth using *Escherichia coli*. In extending this study, Beerstecher & Edmonds (6, 7) have noted that salivary and gastric apoerythein differ in their stability at temperatures of 70 and 100°C. The conclusion, based upon such data, that the apoerythein from the two sources represents different substances does not seem justified since the change in activity with temperature might be due to reaction with other material in the secretions. The effect of heating one secretion with the apoerythein from the other was not reported. Caution in applying the results to true antianemia intrinsic factor is also indicated since Spray (8) has demonstrated a difference between the hemopoietic and the bacterial growth activity of heated intrinsic factor obtained from gastric juice.

Emmelin (9) has presented a complete review of the literature on paralytic salivary secretion. In addition, Emmelin & Muren (10) have demonstrated that "paralytic secretion" produced by section of the chorda tympani nerves, extirpation of the superior cervical ganglion, or injection of cocaine or atropine is accompanied by supersensitivity, not only to epinephrine, but also to norepinephrine and to some other sialogogue drugs. The pharmacologic reactions of the supersensitive gland following section of the chorda tympani nerves were identical to those following chronic treatment with atropine. The histologic changes in the glands in the two conditions were also the same (11).

Gastric Juice.—Milhaud & Epiney (12) have verified the occurrence of two peaks of maximal proteolytic activity in gastric juice from normal persons when tested over a range of pH values. With edestin as substrate, they found that crystalline pepsin also had two pH optimums, one at 2.2 and the other at 3.3. Their attempts to separate crystalline pepsin into two enzymes, however, failed and they were forced to conclude that they were dealing with a single enzyme with dual maximal activity. A group of synthetic peptides in which tyrosine and phenylalanine are linked directly have been prepared by Baker (13) and found by him to be hydrolyzed rapidly by pepsin at an optimal pH of 1.8 to 2.0. This behavior is similar to that when protein is the substrate but quite different from that when other synthetic substrates are employed for they have usually been hydrolyzed slowly at an optimal pH of about 4. A search has been made in gastric juice for an inhibitor of the proteolytic activity of crystalline pepsin and none has been found by Chinn, Book & Beams (14) in the juice of normal persons or patients with duodenal ulcer. Under basal conditions, Janowitz & Hollander (15) found that the mean hourly output of pepsin for normal individuals was 4119 hemoglobin units, while in patients with peptic ulcer it was three times greater. In their tests

there was a significant correlation between the hourly output of acid and the hourly output of pepsin, although in those of Milhaud & Epiney (12) no correlation between the concentrations of the two substances was noted. Another interesting relationship in pepsin metabolism has been established by Janowitz & Hollander (16). Under basal condition in human beings a moderately high, positive correlation was obtained between the average hourly output of pepsin in gastric juice and the average hourly excretion of uropepsin in the urine. The result indicates that determinations of uropepsin may be a satisfactory measure of basal output of pepsin by the gastric mucosa.

The mean concentration of lysozyme in morning gastric juice of 13 fasting medical students was 7.57 μg. per ml. of juice, with a standard deviation of 4.6. While doing these tests, Lobstein & Fogelson (17) found that very low or very high concentrations of sodium chloride reduce the lysozyme activity detectable in gastric juice; they recommended that a constant concentration be maintained if quantitative determinations of the enzyme are desired (18).

Determinations of the electrophoretic pattern of gastric mucin from human and other sources by Pugh, Glass & Wolf (19) confirmed but did not establish the earlier inferences of Glass & Boyd that mucoproteose and glandular mucoprotein are two separate constituents of gastric juice and that mucoprotein is a relatively homogeneous substance. When Glass *et al.* (20) demonstrated that the simultaneous administration of vitamin B_{12} and glandular mucoprotein from gastric juice produced a satisfactory hematopoietic response in seven of nine patients with pernicious anemia, a major step was taken toward establishing that the glandular mucoprotein fraction of dissolved gastric mucin is the main carrier of the intrinsic factor of human gastric juice. When bacterial methods for assay of intrinsic factor are used, differences between the heating reactions of that from gastric and that from salivary sources have been found (6). However, in actual tests, Spray (8) has observed discrepancies between the activity of heated fractions as indicated by tests in patients with pernicious anemia and by tests of bacterial growth, suggesting that the factors assayed by the two methods may not be identical.

Two other factors with important biologic properties are recognizable in gastric mucin. The first, blood group factor A, has been purified to a high degree and determinations by Pardee & Blaker (21) indicate that it is a large, highly asymmetric molecule with a molecular weight of about a million. The second factor produces gastric secretory inhibition when given intravenously. Its output was found by Livermore & Code (22) to be much greater from vagally innervated than from vagally denervated mucosa, and a vagal stimulant such as methacholine caused a greater output than a parietal cell stimulant such as histamine. Further work, such as that of Cambel (23), on the distribution of mucoproteins and mucins in sections of gastric mucosa seems indicated. The delicate fernlike and seaweedlike crystalline structures seen by Hollander (24) in dried smears of mucus secreted from Heidenhain

pouches in dogs have been identified by Watson (25), using roentgen-ray and electron diffraction methods, as sodium chloride mixed with minute quantities of some other unidentified material.

Determinations of ascorbic acid in the wall of the stomach of rats by Breidenbach, Cambel & Ray (26) revealed that the forestomach contained about 15 mg. per 100 gm. and the glandular portion nearly twice as much. The gastritis produced by eugenol reduced the ascorbic acid concentration of the glandular portion until it was about equal to that in the forestomach. The mean concentration of ascorbic acid, as determined by Freeman & Hafkesbring (27), in the gastric juice of more than 100 normal persons was 1 mg. per 100 cc. during fasting and 0.9 mg. per 100 cc. after a test meal of 7 per cent alcohol. No correlation was present between the concentration in gastric juice and that in saliva, blood, or urine. The authors concluded that ascorbic acid is actively secreted by the cells of the gastric mucosa.

Using data from their own and other studies, Glass & Boyd (28) have scrutinized the concept that gastric juice is made of two components, one acid or parietal and the other alkaline or nonparietal. They have concluded that the nonparietal component can no longer be regarded as a uniform entity secreted in response to a single mechanism but should be looked upon as a heterogeneous mixture of several nonparietal gastric secretory products derived from several cellular sources, each capable of secreting at varying rates through separate mechanisms.

Gastric Secretion.—As a result of studying a large number of normal persons and patients with duodenal ulcer, Levin, Kirsner & Palmer (29) have re-emphasized the value of hourly periods of measurement of basal or interdigestive secretion. The hourly output was greater in men than in women. In men it increased with age up to 50 years and thereafter in both sexes it declined. In both sexes and at all ages there was a close parallelism between the basal secretory rate and the response to a standard dose of histamine. The consistency of secretion from hour to hour in individuals was not reported.

The volume and acidity of basal gastric juice secreted by rats after duodenal ligation was the same in tests by Donald & Code (30) whether the juice was drained continuously from the stomach or allowed to accumulate in it. In confirmation of earlier work, acute and chronic vagotomy inhibited greatly or abolished completely the secretion of acid, indicating that in this species acid basal secretion obtained after duodenal ligation is of vagal origin.

Interesting tests of psychic secretion in human beings have been made by Noring (31). Sham feeding, accomplished by chewing but not swallowing two or three sandwiches, was used as the stimulus. The volume of secretion increased rapidly, usually reaching a maximum in the first 10 min. and thereafter declining to basal levels within one hour. Maximal concentrations of chloride, acid, and pepsin were generally attained 30 to 40 min. after the feeding was started. Glass *et al.* (32) have characterized the juice secreted by human beings from 20 until 60 min. after the intravenous injection of insulin.

In their tests, the rate of secretion during this period was unchanged but alterations in the concentration of sodium, chloride, and dissolved mucin did occur if the secretion of acid was stimulated.

In tests by Ambrus, Ambrus & Harrisson (33), pretreatment with repeated daily injections of histamine, with or without associated administration of an antihistaminic, caused no change in the volume of juice secreted by guinea pigs in response to injections of histamine, but did reduce the average concentration of free acid in the juice. Grossman, Robertson & Rosiere (34) have studied the effects on gastric secretion of a series of 62 compounds related to histamine. Three were mildly inhibitory and nine were gastric secretagogues. The finding that one of the nine, 3-β-aminoethyl pyrazole (aminoethylpyrazole), is a suitable and less toxic substitute for histamine has been confirmed by Kirsner *et al.* (35). The topical application of acetylcholine to canine gastric mucosa by Kammerling, Slezak & Grossman (36) sometimes initiated secretion or led to a moderate augmentation of secretion stimulated by histamine.

Gray, Benson & Reifenstein (37), Gray *et al.* (38) and Gray *et al.* (39) have each reported that the administration of ACTH[2] to six persons with normal stomachs and two patients with peptic ulcer for seven to twenty-one days resulted in a rise in the concentration of acid and pepsin in the juice without a change in the volume secreted. The increased output of pepsin in the juice was paralleled by a rise in the 24-hr. output of uropepsin. This confirms the contention of Janowitz & Hollander (16) that determination of the output of uropepsin may be a satisfactory measure of the basal output of pepsin by the gastric mucosa. A similar rise in uropepsin excretion was produced by cortisone given orally or parenterally in doses of 200 to 250 mg./day (37). In two patients, Kirsner, Klotz & Palmer (40) have confirmed the stimulating effect of continued administration of ACTH on the secretion of acid by the stomach. In acute tests with human beings, Ferstl, Heppich & Neugebauer (41) found, however, that giving ACTH and vitamin C between the injections of histamine in a double histamine test reduced the output of acid. In four dogs with various types of pouches the administration of ACTH three times a day for ten to thirteen days by Zubiran, Kark & Dragstedt (42) increased the total daily output of acid from the pouches by 10, 24, 35 and 44 per cent.

Oberhelman *et al.* (43) studied the effects of bilateral transthoracic removal of the sympathetic chains from T-6 or T-7 to and including the splanchnic nerves in dogs with pouches of the entire stomach. The pouches had varying degrees of vagal innervation. Although there was an increase in the mean daily 24-hr. output of gastric juice in seven of the eleven dogs after sympathectomy, and although the majority of those showing an increase responded well to injections of insulin, still it is not clear from the published data that even in this group the increase was significant in more than two or three of the dogs. The gastric secretory response to hypoglycemia caused by the intravenous injection of insulin was increased in all of seven dogs studied.

The sensitivity of the animals to insulin, however, was greatly increased by the operation, probably, as the authors point out, by the concomitant denervation of the adrenal gland. Furthermore, although the dosage of insulin was reduced until the hypoglycemia produced was equal to that which occurred before sympathectomy, the response to insulin was even then so delayed that the possibility of a more prolonged stimulation of the vagal center, as a cause of the increased postoperative secretion rather than an alteration in the secretory reactivity of the gastric mucosa, seems to merit consideration. In two of three dogs studied, the response to a standard dose of histamine increased after sympathectomy. The authors emphasize the augmentation of secretion after sympathectomy and suggest that it may be due to the interruption of gastric secretory inhibitory fibers in the sympathetic nerves.

By means of direct and repeated titration of the acid and base changes produced on either side of an isolated and secreting portion of gastric mucosa of frogs, Teorell (44) has verified that there is a direct correlation and chemical equivalence between the acid formed on the mucosal side and the base found on the muscularis side. He further noted that the mucosal potential had no marked correlation with secretion of hydrochloric acid. In accord with this finding, calculations by Crane & Davies (45), based on estimation of the average hydrochloric acid formation, oxygen utilization, membrane potential, and the electrical resistance of isolated frog gastric mucosa when resting and when secreting hydrochloric acid, indicated that the energy available from electrical processes would not be sufficient for high rates of secretion. They discuss the possibility that some energy for secretion may be derived from basal metabolic sources. Participation of metabolic processes in the formation of acid was clearly demonstrated in the experiments of Davenport & Chavré (46) on the isolated stomach of mice. Their data reveal that when glucose is the metabolic substrate it is only that portion which does not appear as lactate that is concerned directly with the secretion of acid. Furthermore, there is a possible stoicheiometric relation between the acid secreted and this portion of the glucose metabolized. Stimulation of acid production by carbaminoylcholine was apparently accomplished by a change in the reactions through which glucose was metabolized and not by the use of more glucose. The same drug channeled acetoacetate utilization from nonsecretory to secretory mechanisms and thiocyanate and atropine blocked this channeling process indicating that these inhibitors effect definite chemical reactions in the parietal cells.

Experiments by Davies & Edelman (47) revive interest in the possible participation of carbonic anhydrase in the secretory process. They found that the secretion of acid in tied bags of isolated frog and toad gastric mucosa was completely inhibited by high concentrations of certain sulfonamide derivatives. They offer, as explanation of the failure of such substances to inhibit secretion *in vivo*, their calculation that the activity of the enzyme must be almost completely inhibited (more than 99 per cent) before acid secretion is abolished or reduced, and that such degrees of inhibition of enzymes have

not been attained in the *in vivo* tests; indeed, the doses required would be lethal. From determinations of the amount of urea present in secreting isolated gastric mucosa of the mouse and frog and the effects of its addition to such mucosa, Davies & Kornberg (48) have concluded that urea and urease play no direct or catalytic role in the mechanism of acid secretion. Their data, however, allow application of this conclusion to the frog only.

Ray & Jung (49) have established the ionization constants (pKB) of a series of purified basic dyes, the concentration ratios (concentration of dye in gastric juice to concentration in blood) of which were known. Using their ionization constants, they then calculated the ratio of the concentration of the dye in juice to that in blood assuming a simple distribution mechanism. The ratios they obtained were higher than those realized in actual experiments years ago by Ingraham & Visscher. Most recently, Woislawski (50) has found a better correlation between theoretical and actual ratios when the pKB constants of commercial rather than purified dyes were used. The experiments of Ray & Jung (49), however, indicated that some restraining force was opposing the secretion of basic dyes, and that its magnitude increased with basicity of the dye. The phenomenon, they felt, was best explained by the pore theory or concept of a positively charged membrane between the blood and gastric juice as developed previously by Ingraham & Visscher. Ray & Jung (49) calculated a factor which enabled them to assign some measure to the restraining force at the mucosa. Their formula needs validation. Its use, however, has led to the selection and testing of three new dyestuffs by Ray & Peters (51). The dyes were potential carcinogens. Two of the three were secreted rapidly in the stomach of rats with duodenal ligation. No results of carcinogenicity have yet been reported.

Gastric Secretory Inhibition.—A number of cholinergic blocking agents have been studied in relation to their ability to inhibit gastric secretion (52 to 65). The results of Hunt, Macdonald & Spurrell (66) confirmed, in normal human beings, the earlier observation that gastric secretion is reduced by the ingestion of large quantities of sugar. Hawk & Hundley (67) demonstrated that the volume and acidity of gastric secretion in rats with duodenal ligation were moderately reduced by prior feeding of diets deficient in thyamine or pyridoxine.

Baisset *et al.* (68) confirmed that transthoracic vagotomy in dogs reduces the secretory response of gastric pouches to various test meals and to stimulation by histamine and pilocarpine. During their tests, peptic activity in the juice of two Hollander-Jemerin type of pouches was reduced by vagotomy although it was unaffected in juice derived from a Pavlov type of pouch. Also, in confirmation of earlier work, Antia *et al.* (69) demonstrated, in a careful study of secretion from the intact stomach of dogs, that simple section of the vagi just above the diaphragm abolished the secretory response to insulin and to 16A [5(γ,γ-dimethylallyl)-5-ethylbarbituric acid] although the secretory capacity of the stomach was unaffected and the response to urethane β-methylcholine (Urecholine) actually was increased. Basal or inter-

digestive secretion was small in amount and unchanged by the vagotomy, a result in direct contrast to that of Dragstedt & co-workers who have tested the effects of vagotomy on innervated pouches of the entire stomach. The results of Antia and co-workers (69) prove once again that the basal secretion of such pouches is abnormally high, possibly because the pouches lack the inhibitory influence of acid in the duodenum.

In human beings, Grimson, Rowe & Taylor (70) confirmed that vagotomy reduces or abolishes the secretory response to administration of insulin and that if a response does occur, indicating incomplete vagotomy, it takes place later than in persons with intact vagi. Likewise, the finding in dogs that the concentration of pepsin in gastric juice may be unaffected by vagotomy has been extended by Book, Chinn & Beams (71) to include human beings. The prospect of return of vagal function after operation has been the subject of studies by Stein & Meyer (72) and by Dragstedt, Oberhelman & Woodward (73). Recovery of traumatized, but possibly undivided fibers, seemed to require about six months to one year and thereafter the status changed little. Complete restoration of vagal function sometimes occurred, but in the majority of individuals incomplete or no recovery was evident one to seven years after the operation. Even in those showing some return of the response to insulin, basal secretion and the secretion in response to histamine and caffeine were much reduced.

The most certain way to reduce the output of gastric juice is to remove part or all of the gastric mucosa. Partial gastrectomy produced a persistent achlorhydric response to a Rehfuss test meal in more than half of the patients studied by Cornell & Druckerman (74). It also caused a significant reduction in the volume and in the concentration of acid and chloride, but not in the concentration of pepsin in the juice obtained by Noring (75) in response to sham feeding. Striking reductions were obtained by Farmer *et al.* (76) in the volume and acidity of juice secreted under a variety of circumstances when vagotomy was combined with resection of one half of the stomach.

In tests by Lobstein & Fogelson (77) histamine-stimulated gastric secretion in dogs was partly inhibited by the oral administration of a detergent complex (RO11). These authors (78) also reported that mixing the detergent with mucin prolonged its action. Pretreatment of guinea pigs with histamine was found by Ambrus, Ambrus & Harrisson (79) to produce some reduction in the free acidity, little in the total and none in the volume of juice secreted in response to histamine. Tomenius & Paulsen (80) demonstrated in one subject that doses of chorionic gonadotropin ranging from 900 to 20,000 I.U. produced a reduction in gastric secretion stimulated by histamine or insulin. Results of tests with a preparation of enterogastrone which contained small amounts of pyrogens indicated to Linde, Öbrink & Ulfendahl (81) that the effect of the preparation on parietal secretion was one of inhibition of volume output only. Local anesthetization of the throat was found by Friedrich & Fóti (82) to have no effect on the secretory response of the stomach to caffeine. When Benjamin & Ivy (83) gave repeated small feedings of milk and

cream alone or mixed with calcium carbonate to patients with duodenal ulcer, gastric secretion was increased and little neutralization was produced. When the calcium carbonate was replaced by sodium bicarbonate, stimulation of secretion still occurred but neutralization of the gastric contents was accomplished.

Pancreatic Secretion.—Demonstration of the independence of the dextrinogenic (starch-liquifying) and saccharogenic (reducing-substance-liberating) actions of canine pancreatic juice by Waldron (84) suggested to him the presence of two amylolytic enzymes. Sedimentation and diffusion studies by Smith, Brown & Laskowski (85) indicate that the various crystalline trypsins are all of about the same size and shape with calculated molecular weights of 22,500. Byrne *et al.* (86) confirmed the finding of Munro & Thomas that the protein components of pancreatic juice are secreted in constant proportions even when meals of widely differing composition are fed. Six to ten components were demonstrated electrophoretically and lipolytic, amylolytic, and proteolytic activities localized in different components of the pattern (86, 87).

Bosshardt, Ciceresko & Barnes (88) prepared an extract of frozen beef pancreas which, when fed to insulin-maintained-depancreatized dogs, prevented the development of fatty livers. Its lipotropic activity could not, however, be accounted for upon the basis of its content of choline, methionine, or inositol. Rhoads *et al.* (89) verified the presence of the activity in the extract and found that it was destroyed by boiling. Haanes & György (90) made the interesting discovery that the extract does contain an active proteolytic enzyme closely resembling trypsin, but that its presence was completely masked in ordinary tests for such activity by a potent inhibitor. The explanation of the lipotropic action of the extracts rests with their finding that the addition of duodenal succus entericus from depancreatized dogs completely abolished the action of the inhibitor. Thus, in the duodenum of the depancreatized dog, the proteolytic action of the liberated enzyme would release, as trypsin will, sufficient methionine during the digestion of protein to prevent the development of a fatty liver.

In a series of careful experiments, Brooks & Thomas (91) showed that when equal amounts of HCl as 0.1 *N* solution or as gastric juice were placed in the duodenum equal amounts of pancreatic juice were secreted, indicating clearly that gastric juice contains no pancreatic stimulant other than hydrochloric acid. Annis & Hallenbeck (92) demonstrated in dogs that removal of all pancreatic juice secreted in response to a meal of meat resulted in a much more voluminous output of juice than when the juice was replaced in the duodenum. Substituting saline solution in the duodenum for the juice had no effect on the excessive secretion while replacement with bicarbonate solution restored secretion to normal. Failure of alkalinization of the duodenum to abolish the customary prandial response indicated that this secretion did not arise from excitation of the secretin mechanism, while abolition of the excessive secretion by the same procedure suggested that the excessive

secretion was due to liberation of secretin. A histologic study of the pancreas of various species by Grossman, Wang & Wang (93) indicated that centroacinar cells and cells of the intralobular ducts secrete alkaline phosphatase into pancreatic juice. In acute and in one chronic experiment in dogs, Thistlethwaite (94) found that spontaneous and prandial pancreatic secretion were reduced by 20 to 34 per cent after vagotomy while in a human being Dreiling, Druckerman & Hollander (95) showed that secretin-stimulated pancreatic secretion was unaltered by vagotomy.

Annis & Hallenbeck (96) demonstrated a decisive reduction in the volume, bicarbonate and nitrogen content of pancreatic juice secreted in response to a standard meat meal after resection of three fourths of the stomach of dogs, although the response to acid placed in the duodenum or to secretin injected intravenously was unchanged by the operation. Alimentary starvation of 11 days by a patient with a fistula of the pancreatic duct was found by Hildes, Ferguson & Bartlett (97) to reduce greatly the volume of juice collected but not to effect its concentration of electrolytes. In a study by Rauch & Stenstrom (98) the volume and pH of canine pancreatic juice secreted in response to the administration of 100 cc. of 0.1 *N* HCl placed in the stomach were unaffected by roentgen-ray radiation delivered over the pancreas, but the concentrations of amylase, lipase, and trypsin were significantly lowered by the irradiation.

Enteric Secretion.—In a patient studied by Heifetz (99) pure succus entericus collected from an isolated segment of small bowel never contained diastase even though the concentration of diastase in the blood was often high. At body temperatures, Hartiala & Grossman (100) observed a rapid, spontaneous loss of viscosity in canine duodenal mucus. This was reduced by cooling to 10°C., accelerated by cysteine, glutathione, and proteolytic enzymes but unaffected by a variety of common ions and by lysozyme, hyaluronidase, pectinase, and glucuronidase. The loss of viscosity was accompanied by a rise in concentration of nonprotein nitrogen with no change in reducing substances, glucuronic acid or acetylglucosamine.

A crystalline product, presumably enterocrinin, was isolated by a complicated procedure from acid extracts of mucosa of hog's small intestine by Heggeness & Nasset (101). Small doses of the substance stimulated secretion of succus entericus, while large doses did not and were toxic. In confirmation of earlier work, histamine was found by Koskowski & Mahfouz (102) to stimulate secretion from Thiry-Vella fistulas of loops of the upper part of the small bowel in dogs. Prior administration of pyranisamine Neo Antergan delayed onset of secretion and greatly reduced its volume and invertase activity—an interesting result since such drugs have no effect on histamine-induced gastric secretion. Histamine-like activity has been found in crude extracts of the wall of the entire digestive tract of dogs by Douglas *et al.* (103). The greatest amounts were present in the upper part of the small bowel with a declining gradient from duodenum to anus, and the greatest

concentration in the different layers of the wall was uniformly in the mucosa. The concentration of xanthine oxidase in extracts of the small bowel of rats was found by Westerfield & Richert (104) to be dependent upon the simultaneous provision of a diet adequate in protein and in an unidentified liver-residue fraction.

Bile and Bile Duct System.—Unchanged thyroxine was the principal I^{131}-containing substance found in the bile by Taurog, Briggs & Chaikoff (105) during the first hour after the intravenous injection of I^{131}-labeled L-thyroxine in rats. Later an unidentified I^{131}-containing substance appeared and in 3 hr. it accounted for most of the I^{131} in the bile. McConnell & Martin (106) detected about 2.5 per cent of the total radioselenium they gave to rats intraperitoneally in the bile in 48 hr. Brauer, Pessotti & Pizzolato (107) have developed a promising technique for the perfusion of isolated livers of rats. They have demonstrated that the preparation can be maintained under conditions which permit the continuous production of bile for periods up to 25 hr.

Baronofsky & Gaviser (108) observed a more nearly normal emptying of the gallbladder in cats after partial gastrectomy when continuity of the bowel was re-established by a short rather than a long duodenojejunal loop. Haley & Bassin (109) demonstrated that isolated guinea pig gallbladder and common bile duct system suspended in Tyrode's solution form a suitable preparation for the assay of substances which counteract the contractions of smooth muscle produced by histamine or acetylcholine.

The pressure which must be applied to fluid in the common bile duct before it will pass into the duodenum is often referred to as the resistance of the sphincter of Oddi and used as a measure of its tonic state. In acute experiments in dogs, Thistlethwaite (94) found that the resistance of the sphincter was abolished by application of 2 per cent solution of procaine, reduced by section or block of the thoracic sympathetic chains and unaffected by vagotomy or Banthine. Shingleton, Anlyan & Hart (110) have verified that vagotomy does not affect the resistance of the sphincter in acute experiments in dogs and cats. They were able to induce a spasm in the sphincter which caused a reproducible increase in sphincteric resistance, by perfusing dilute (0.01 *N*) HCl through the ampulla of Vater. This spasm behaved differently from the ordinary tone of the sphincter. It was unaffected by preganglionic sympathectomy or sympathetic block by Regitine but it was abolished by vagal block following section of the nerves or administration of methantheline and by sympathetic block following celiac ganglionectomy or by administration of tetraethylammonium compounds. Smith, Walters & Beal (111) have measured sphincteric resistance in patients by perfusion through the common bile duct. The intravenous injection of 10 mg. of morphine uniformly increased the resistance, and atropine or methantheline given intravenously reduced the spasm but could not abolish it nor completely prevent its development.

Digestion

In a study by Everson (112) the addition of a powdery preparation of pancreatic enzymes (pancreatin) to the diet of dogs with total gastrectomy reduced losses of nitrogen but not of fat in the stools. Merten (113, 114) has reported improved retention of nitrogen in patients and two normal persons when acid and preparations of gastric enzymes were administered. Sodium taurocholate and desoxycholate were found by Christensen (115) to accelerate greatly the peptic and tryptic hydrolysis of native but not denatured egg albumin and lactoglobulin. The suggestion was made that bile salts may thus aid in the digestion of native proteins in the diet by accelerating their denaturation, which is the first step in their degradation. The point was also made that fully denatured protein substrates should always be used for determination of the proteolytic activity of gastrointestinal juices because, if native and not denatured proteins were used, varying quantities of bile could cause variations in apparent proteolytic activity quite independently of the actual amount of enzyme present.

Calandra, Hardt & Stanish (116) have identified a large number of substances capable of inhibiting tryptic digestion *in vitro* and have discussed the possible therapeutic usefulness of such substances. In a study by Schulman (117) of the liberation of I^{131} from labeled fibrin by trypsin, chymotrypsin, and plasmin, the presence of an inhibitor in plasma was confirmed and its concentration in a variety of pathologic conditions was estimated. Heilskov (118) found lactose in the wall of the small bowel but none in the pancreas or colon of young cows and rabbits and human fetuses. The amount present in the small bowel declined rapidly as the ages of the animals increased. In large groups of normal subjects, Smith & Roe (119) found that the 24-hr. excretion of urinary amylase was decreased by a high carbohydrate diet and increased by a high protein diet and by fasting.

Motility

General Aspects.—Adequate methods for the recording of pressures throughout the alimentary canal are now available and have been fully described by Brody & Quigley (120) and found satisfactory in tests by Bachrach, Brody & Drury (121) and Hightower (122).

The name, "substance P," was given by Gaddum & Schild many years ago to an unknown substance recognized first by Euler & Gaddum in extracts of the muscle coat of the small intestine. They found that it produced slow contractions in the isolated gut and Euler suggested that it might be responsible for spontaneous movements of the intestine. The distribution of substance P in the alimentary canal was studied during the past year by Douglas *et al.* (103) in dogs, and by Pernow (123) in a variety of other animals. In dogs, there was little or no substance P in extracts of the esophagus; there was some in extracts of the stomach and a good deal in those prepared from small and large bowel. Extracts of the upper part of the small bowel

were more active than those from the lower part. A similar gradient was found in the gastrointestinal tracts of cats, pigs, oxen, and sheep. In these animals the greatest amounts of substance P were found in the uppermost portions of the small and large bowel, about one half as much in the stomach and one third as much in the lower part of the small bowel. The distribution between the different layers of the wall of the gut is not the same in all animals (123) but in the dog (103) and the horse, in which the most careful separations have been accomplished, the greatest concentration was found in the muscularis mucosae. Ellis & Rasmussen (124) presented pharmacologic evidence that some contractions of isolated portions of rabbit's intestine and of dog's muscularis mucosae were mediated through nerves but not by the liberation of a cholinergic or adrenergic mediator or by histamine, but by some other yet unknown neurohumoral agent.

In tests by Furchgott & Wales (125), the ability of compounds of the Krebs' cycle to restore activity in substrate-depleted segments of rabbit's intestine indicated that the Krebs' cycle played a major role in the intermediary energy metabolism of the smooth muscle. In experiments of Scow & Foglia (126), reductions in the over-all basal metabolic rate of rats by complete thyroidectomy did not affect the rate of passage of a barium meal through the gastrointestinal tract.

Swallowing and Esophageal Motility.—Doty (127) made a careful analysis of the electrical characteristics of repetitive stimuli which will evoke reflexly the pharyngeal component of swallowing when applied to the superior laryngeal nerve of anesthetized dogs. An optimal frequency of stimulation was obtained at which deglutition was elicited with the shortest latency, lowest threshold, and most rapid continuing rate. Use of patterned stimuli, composed of repeated groups of identical electrical pulses, indicated that, at the frequencies used, each pulse was effective irrespective of when it was delivered, provided it was within the optimal pulse interval for the reflex. Under some circumstances unilateral behavior of the central mechanism was observed. Many of the results of the study are difficult to interpret, but tests of this type are essential if the central mechanisms of this and other alimentary reflexes are to be understood.

Jefferson *et al.* (128) demonstrated an important distinction between section of the vagus nerves just below the hilus of the lung, accompanied by separation of the trunks from the esophagus below this point, and section of the vagi just above the diaphragm. In the dogs they studied, the higher section (with separation) was followed by cardiospasm and esophageal retention in every animal. These were preventable by simultaneous section of the left phrenic nerve. Vagotomy just above the diaphragm was not followed by any disturbance of the esophagus or the cardia. The results have bearing upon those obtained by Donald (129) in the rat. He found that bilateral vagotomy above the root of the lung caused complete paralysis of the esophagus and death. Section of the nerves, however, just above or below the diaphragm did not paralyze the esophagus but led to its pro-

nounced dilatation. In the rat, the stomach clearly participated in the development of the dilatation for it was prevented by gastric resection and made worse by operations designed to render the cardia more patent. Berman (130) found it possible to replace segments of the esophagus in dogs with plastic tubes. In one instance, the fibrous sheath surrounding the tube was sufficiently developed in about one year to allow removal of the tube with survival of the animal.

Vomiting.—Dogs in which Wang & Borison (131) produced bilateral lesions in the dorsolateral portion of the reticular formation of the medulla oblongata by implantation of radon seeds, did not vomit when given apomorphine intravenously, and were refractory to large doses of copper sulfate placed in the stomach. The experiments indicate localization of the vomiting center in the medullary reticular formation. Borison (132) showed, in confirmation of others, that stimulation of the emetic chemoreceptor trigger zone in the lateral posterior portion of the medulla of the cat by direct action of the glucosides of digitalis, accounts for early (within 30 min.) digitalis-induced vomiting. His experiments indicated also that a second peripheral mechanism was responsible for late vomiting.

Gastric Motility.—With a balloon-water manometer type of recording system, Bachrach, Mason & Pollard (133) recognized type I waves (tonus rhythm), type II waves (hunger contractions or peristaltic waves), and type III waves (gastric tetany) in records obtained from the body of the stomach of human beings, and noted that the pattern of their occurrence and their dimensions were similar in normal persons and in patients with duodenal ulcer. About five years ago Kay (see Doret, 134) reported that the inhibition of motor activity of the stomach, which occurs quite regularly in normal persons when water is swallowed, was lacking in patients with duodenal ulcer. In 1951, Doret (134) was unable to confirm the observation and concluded that lack of inhibition upon swallowing water was not specific for duodenal ulcer.

In an interesting study of the contractions occurring in isolated stomachs of frogs and isolated segments and rings of the stomach wall, Frank (135) demonstrated that the origin of the periodic or rhythmic contractions of the whole stomach did not lie in one particular spot or site, but was a property of each isolated segment. His results indicate that more complicated movements of the stomach may arise from co-ordination or interference between adjacent areas. The emptying of the stomach of human beings was shown to be slowed by the addition of sucrose to a standard test meal (66). The introduction of acid solutions into the duodenum was also found by Bassi & Lorenzini (136) to inhibit gastric motility. In their tests, 5 to 10 cc. of 0.1 *N* HCl placed in the duodenum always caused prompt cessation of all peristaltic movements as recorded from a balloon in the stomach.

In dogs, after resection of the lower 3 to 4 cm. of the thoracic vagus nerves, Quigley & Loucks (137) observed the usual immediate changes in the stomach of slower evacuation, reduced tone and motility in the body,

retention and vomiting. Three to four weeks later the delayed onset of evacuation had disappeared. Persistent sequelae in the stomach were the evacuation of smaller boluses into the duodenum and less frequent propulsive contractions associated with some gastric retention. Weckesser *et al.* (138) have likewise observed a permanent delay in gastric emptying time after vagotomy. In patients with peptic ulcer, results of roentgenologic studies by Walters, Priestley & Belding (139) indicated some recovery of motility from the immediate effects of vagotomy with the passage of time.

Motility of the Small Bowel.—In tests by Furchgott & Wales (140), lowering the pH of the perfusion fluid surrounding isolated segments of rabbit jejunum from 7.4 to 5.4 markedly reduced the amplitude and frequency of the rhythmic contractions. When the contractile activity of the preparation was allowed to decline in a substrate-free medium, complete restoration of amplitude of contraction occurred upon the addition of glucose or pyruvate and about 70 per cent restoration occurred when acetate was added. Glucose and pyruvate were certainly suitable substrates for the metabolic processes involved in the contractile mechanism.

When Mohamed & Bean (141) increased the carbon dioxide content of blood perfusing an isolated segment of dog's small bowel, rhythmic contractions (type I) and tonus were usually initially augmented and then both were inhibited. Van Liere, Stickney & Northup (142) found that the propulsive motility in pups was decreased by anoxic anoxia while that of adult dogs was unaffected. Anemic anoxia did not alter the motility in pups. A correlation has been demonstrated by Stickney, Van Liere & Northup (143) between the length of the small intestine of rats and dogs and the distance a feeding of charcoal in acacia traverses in a given time. In their study, the longer the small bowel, the greater the distance the meal traveled in a fixed interval, but the proportion of the intestine traversed by the meal in that time was about the same in all animals.

With recording balloons in the stomach and duodenum, Abbott, Mack & Wolf (144) studied the occurrence of duodenal spasm under a variety of conditions in human beings. Their records, and those of others made earlier, clearly show that the so-called spasm consists of a sustained type III contraction of the duodenum upon which are superimposed rhythmic type I contractions. The authors found that this complex was by no means an invariable accompaniment of nausea nor was its occurrence particularly well correlated with distressful or painful mental or physical experiences. The portion of the duodenum involved was emptied by the spasm, material moving back into the stomach as well as distally in the bowel. During the spasm, hypomotility and hypotonus were invariably present in the stomach. In its complete form the complex obviously represents a co-ordinated reaction. The mechanisms involved are not known.

Motility of the Large Bowel.—A careful classification and analysis of the types of waves seen in records of motor activity of the pelvic colon of normal persons has been made by Spriggs *et al.* (145). In fasting individuals, the

bowel was active about one third and quiescent about two thirds of the time. Most of the activity was due to type II mixing or haustral waves. No propulsive, type IV (mass movement) activity was registered in normal persons although it was frequently seen in records from patients with ulcerative colitis. These large, mass movement, type IV waves were also seen in records obtained by Kern *et al.* (146) from a large series of patients with ulcerative colitis. Both groups of workers reported on the reduced number of mixing, nonpropulsive type II waves in the records of patients with this disease.

Grace, Wolf & Wolff (147) have published a small monograph on the motor and other reactions of the colon as seen directly in four fistulous subjects under a variety of circumstances.

Absorption

Little work on the relation of absorption to motility has been done. Goodman *et al.* (148) have developed a concept of gastrointestinal transit which they define as that fraction of the quantity of material contained in a portion of the gastrointestinal tract (stomach, small or large bowel) which is delivered to the adjacent distal portion per unit of time. Their theoretical and practical application of the concept to the disappearance of Evans blue dye in the alimentary canal of rats has allowed measurement of what they refer to as maximal limit of absorption availability. Goodman, Lewis & Schuck (149) have used this to test the effect of roentgen radiation on the gastrointestinal tract of rats. They observed a reduced absorption availability because of slowing in the emptying of the stomach. The usefulness of their measurement will require further validation, but it has immediate value by forcing consideration of the relationship between motor activity and absorption.

Blickenstaff *et al.* (150) found that the absorption of water and chloride from a 0.9 per cent solution of sodium chloride was most rapid from the small bowel of dogs when the hydrostatic pressure was maintained at 20 or 30 cm. of the saline solution. In two of the three dogs studied, pressures greater than optimal actually reduced absorption. The optimal pressures reported occur naturally during normal motor activity and no doubt motor activity does affect absorption, but the relationship between the two has not been sufficiently studied.

Adolph & Northrop (151) have contrasted the disappearance of water and chloride in hypotonic and hypertonic solutions when placed in the alimentary canal and when placed in the peritoneal cavity of rats. Absorption of sea water (the hypertonic solution used) from the alimentary canal was much slower than that of distilled water. Part of the delay was due to retention in the stomach, and part to rapid dilution of the sea water in the small bowel with water drawn from elsewhere in the body. The rate of absorption of water from the peritoneal cavity was the same whether distilled or 0.1 *M* solutions of sodium chloride were used, but absorption was delayed when sea water was employed. No matter what solution was used, however, loss of excess water by diuresis was slower when the fluid was placed in the peri-

toneal cavity than when placed in the alimentary canal. A further protective effect of alimentation was apparent in the low incidence of hemolysis after massive oral as contrasted to intraperitoneal administration of water. Others (150) have found that water is absorbed more rapidly from loops of small bowel of dogs when it is in the form of dilute rather than in the form of strong solutions of sodium chloride, though no such relationship was evident with respect to the rate of chloride absorption. Wollaeger & Scribner (152) identified an abnormal retention of water, or failure of its absorption, during digestion in patients with nontropical sprue.

Thyroidectomy in rats produced a significant slowing in the rate of glucose absorption (126). Verzár & Sailer (153) found that adrenalectomy had the same effect in rats and, in addition, it reduced the concentration of alkaline phosphatase in the mucosa of the small bowel. They interpreted the coincidence as indicating a direct relationship between alkaline phosphatase in the mucosa and the selective absorption of glucose by the mucosa. Their observations were strengthened by their study with Richterich (154) in which by histologic and chemical methods a decline of alkaline phosphatase in the cells of the mucosa was demonstrated after adrenalectomy, and regeneration after treatment with cortisone, adrenal extract, or desoxycorticosterone. Parallel studies with thyroidectomy were not reported. An interesting, though somewhat conflicting, contrast was made between the hogfish and the rat by Cordier & Chanel (155). They found that the absorption of glucose was more rapid in the hogfish, although Hele (156) demonstrated that phosphorylation of glucose by homogenates of the intestinal mucosa of the two species was the same or very similar. All seemed agreed, however that absorption of glucose occurs mainly in the small bowel. In this regard the stomach may play a protective role, for de Laet & Van den Broucke (157) demonstrated that hypoglycemia (concentration of glucose less than 60 mg. per 100 cc.) occurred in about half of the patients with gastrectomy when they ingested 100 gm. of glucose. The hypoglycemia, they suggest, may be due to reduced glycogenolysis in the liver following the rapid and massive absorption of sugar brought to the liver via the portal vein. The concept is similar to that developed earlier in the year by Butler (158). He found hypoglycemic reactions under ordinary living conditions in only about 5 per cent of patients with gastrectomy, but those who displayed reactions were found more resistant than normal persons to the action of epinephrine in increasing the concentration of blood sugar. The result led him to suggest that the cause of postgastrectomy hypoglycemic reactions may be a temporary postprandial inhibition of glycogenolysis in the liver.

The absorption of D-xylose was more consistent than that of glucose or fructose in a series of normal persons studied by Brien and co-workers (159). Changes in organic phosphate in the plasma during absorption indicated that phosphorylation of D-xylose occurred. If this proves to be the case, D-xylose would then be a very suitable substance with which to study disordered absorption of carbohydrate.

The question, "Are triglycerides hydrolyzed before absorption?" has been

resolved, in part at least, by an important study of Reiser *et al.* (160). They found that 25 to 45 per cent of the labeled trilinolein they fed rats was hydrolyzed to its constituent parts during absorption. The glycerol so formed was not reused in the synthesis of glycerides found in the lymph and the occurrence of $C^{14}O_2$ in air expired by the rats indicated that some was promptly metabolized. Most of the triglyceride which had not been completely hydrolyzed and which appeared in the lymph had apparently been hydrolyzed to the monoglyceride, absorbed as such, and then resynthetized to triglyceride.

Bloom, Chaikoff & Reinhardt (161) have demonstrated that the rate and route of fatty acid absorption in the rat depends upon the length of the carbon chain of the acids. The member of their series with the longest chain, stearic acid (C_{18}), was absorbed much more slowly and more exclusively via the lymph system than were the shorter-chained members. The members with fewer carbon atoms, lauric and decenoic (C_{14} and C_{10}) acids, besides being absorbed more rapidly, apparently took routes other than the lymph, for only small amounts of them were found in it. The assumption was made that the decenoic acid, which had disappeared from the gut, had left via the portal circulation. Since little of it was recovered in the liver and tests for it elsewhere were not made, final conclusions should, it seems, await satisfactory demonstration that it had not been destroyed.

Biggs, Friedman & Byers (162) have verified the finding of others that in rats only a small part of ingested cholesterol is absorbed. Almost all of that which was absorbed in their tests was recovered in the lymph. Absorption of fat in dogs with biliary fistulas was improved greatly, in tests by Searle & Annegers (163), when they gave ox-bile extract, sodium taurocholate, or sodium glycocholate by oral or duodenal administration, but was unaffected when oxidized cholic acid was used. When bile was excluded from the gastrointestinal tract of dogs, Bernhard, Ritzel & Hug (164) found the lipids in the feces composed of a mixture of ingested fat and body fat excreted into the intestinal lumen. Between 50 and 80 per cent of the deuterium-labeled fat they fed to their dogs was absorbed.

The importance of the presence of the stomach in the absorption of fat has been demonstrated by Everson (165) in a thorough metabolic study in dogs. Using a standard diet he showed that the average per cent of ingested fat in the stools rose from 2.8 in intact, to 27.6 in gastrectomized animals. Similar import can be ascribed to the small bowel. Resection of the proximal or the distal two thirds of the small bowel of dogs was followed by excessive losses of fat in the stools (138). Vagotomy, if done soon, only temporarily improved absorption of fat and, if done many weeks after resection, had no effect on the losses of fat in the stools. Chylomicron counts and nephelometric determinations on serum removed after ingestion of fatty meals indicated to Marder *et al.* (166) slower absorption of fat in aged than in young people. Results of a study by Brien *et al.* (167) in which Tween 80 was ingested indicated that the detergent may hasten absorption of fat in normal persons.

In a study by Matthews & Smyth (168), blood from a loop of ileum in which DL-alanine had been placed contained up to three times as much L-alanine as D-alanine. The result supports the concept of the existence of an active stereochemically specific mechanism in the intestinal wall for the absorption of L-amino acids—its site is most likely the mucosa. Kamin & Handler (169) found that in rats the presence of an excess of an amino acid almost invariably inhibited the intestinal absorption of another amino acid, and that the nature of the competing amino acid was of little consequence. The presence of hypoproteinemia in patients, Hardy & Schultz (170) found, did not alter much the absorption of a casein hydrolysate from segments of jejunum. However, gastrectomy in dogs increased fecal loss of nitrogen from 13 to 42 per cent (165), and resection of two thirds of the small bowel caused increased quantities of nitrogen to appear in the stools (138).

Thompson, Lewis & Alving (171) have made a detailed study of absorption and excretion in the terminal 6 feet of ileum in two patients in whom the segment of bowel was isolated for treatment of renal failure. The volumes of the fluid they introduced and recovered were nearly equal. Urea was excreted and glucose was absorbed. Sodium was absorbed even against a considerable gradient. Calcium was excreted into the perfusion or rinsing fluid even against a tenfold gradient produced by raising the concentration in the perfusate. The accumulation of sodium in the body and the loss of calcium from it were of sufficient magnitude to produce edema and hypocalcemic tetany respectively. Potassium consistently passed into the perfusate but its loss did not reach clinically significant proportions. The results confirm some earlier studies on animals, and support the concept of a rather rigid pattern of electrolyte exchanges in different portions of the gastrointestinal tract.

The amounts of sodium held in the stools of normal persons and edema-accumulating patients following ingestion of carboxylic resin as well as the amounts in sweat and saliva were determined by Berger & Steele (172). With ingestion of the resin there was much less sodium in the stools of the patients with edema than in the stools of normal persons. The result was interpreted as indicating an increased reabsorption of sodium in the colon by the patients. The conclusion may be correct, but in the absence of data to show that the amounts of sodium excreted into the small bowel and delivered by it to the large bowel were the same in both groups of individuals, caution of interpretation is indicated. The salivary and sweat concentrations of sodium were also lower in the patients. The three differences suggested to the authors that the patients had an altered transfer of sodium which limited its loss from the body. This could be most easily explained as being the result of a disturbed humoral control of sodium excretion which might be caused by excessive action of the salt and water hormone of the adrenal glands.

In isolated segments of guinea pig small intestine a barrier at the mucosa to the passage of histamine has been found by Dworetzky & Code (173), and its dependence upon the viability of the gut and its independence of histaminase have been demonstrated. Some ionic exchange resins and magnesium

and sodium sulfate have been found by MacDonald *et al.* (174) to limit the absorption of ingested strontium. The simultaneous oral administration of hydrated alumina, as a gel or as a powder, with a number of different cholinergic blocking agents was found by Seifter and co-workers (175) to prolong the action of the drugs. The absorbent apparently acted as an intestinal repository. Some mineral oil was apparently absorbed from the gastrointestinal tract of growing rats in tests made by Bernhard & Scheitlin (176).

Excretion

Mention has already been made of the study by Thompson, Lewis & Alving (171) in which it was shown that urea, calcium, and potassium constantly passed into the fluid used to perfuse the isolated terminal 6 feet of ileum in two patients. A similar, though less detailed, study has been made by Sloan (177) in uremic and nonuremic dogs using 3 to 4 feet of the midregion of the small bowel. He has demonstrated too that urea passes into the rinsing or perfusion fluid. He also found that parenterally administered creatinine appeared promptly in the perfusate and that if the perfusate was hypotonic the dogs gained weight, if hypertonic weight was lost, and if isotonic no change in weight occurred. Other shifts which he did not measure were occurring in some of his dogs, for he mentions that calcium gluconate was administered parenterally for convulsions. It is likely that in the dogs, as in the patients (171), calcium was being excreted continuously by the small bowel.

Miscellaneous

Gastrointestinal Circulation.—The volume of blood in the splanchnic bed of unanesthetized dogs was found by Delorme *et al.* (178) to be between 20 and 50 per cent of the total blood volume. Estimates were also made of the volumes in the intestinal, hepatic, splenic, and gastric components of the splanchnic bed. When the blood, perfusing an isolated segment of dog's bowel, was made hypercapnic by equilibration with 6.7 to 15 per cent carbon dioxide there was, in tests by Mohamed & Bean (141), a consistent increase in blood flow through the segment due to local vascular dilatation. When the animal breathed air containing a high percentage of carbon dioxide but the segment was perfused with blood containing little carbon dioxide, a reflex or centrally induced vasoconstrictive response occurred which was never as intense or as prompt as the dilating action of high local concentrations of carbon dioxide. Hypocapnia, in the blood perfusing the isolated segment, always resulted in a diminution of blood flow through the segment. The experiments also clearly show that blood flow through the intestine is profoundly affected by intestinal motor activity. For example, the authors were able to detect the effects of carbon dioxide on blood flow only when the motility was not seriously affected.

Grayson (179) has subjected thermocouple methods for determination of blood flow in the bowel to critical analysis. He has demonstrated that the

relation of temperature to flow is not direct and that this and other factors make precise quantitation by the method difficult. Still, changes can be followed qualitatively and for this he recommends the use of a thermocouple heated to a temperature greater than that of the body, with both the heated and the cold junction placed in the bowel.

Gastrointestinal pH.—Rovelstad, Owen & Magath (180) have studied the feasibility of continuously recording the pH in the upper part of the gastrointestinal tract of human beings by means of a swallowed glass electrode. Errors introduced by potentials generated by factors other than pH were assessed. Preliminary findings showed that satisfactory measurements could be made, that wide and rapid spontaneous fluctuations in pH occurred in the antral end of the stomach, and that these fluctuations were also present in both the antrum and the duodenum when histamine was given.

Digestive Systems of Ruminants and the Horse.—The abomasum is the secretory or glandular part of the ruminal stomach. Masson & Phillipson (181) have pioneered in the study of its secretory function by preparing two vagally innervated pouches of it in sheep. One was of the Pavlov type, and the other of the Hollander-Jemerin type. The latter was the more successful and a copious flow of juice, amounting to about 1 l. per day, was obtained when the sheep was fed. The chloride content of the juice was quite constant at about 158 m.eq. per l., and the acidity averaged 86 m.eq. per l. in prandial juice and 51 in fasting juice.

The substrate requirements of the microflora of the bovine rumen and the principal products resulting from their action on various sugars have been established by McNaught (182). Experiments by McDonald (183) have confirmed earlier findings that ammonia is present in the rumen of sheep. He also showed that the ammonia is derived not only from urea in saliva but also from urea formed during breakdown of protein by the microorganisms of the rumen and finally, that ammonia is utilized by the ruminal microflora for growth.

In the suckling ruminant, liquids such as milk, after being swallowed, pass directly to the abomasum or secretory portion of the stomach via the esophageal groove and the omasal canal. By this means the fermentation chambers, the reticulum, and the rumen, are bypassed. Comline & Titchen (184) have made a thorough study of the movements of the esophageal groove in decerebrate calves and lambs. Contractions of the lips of the groove, which convert it into a canal, were recorded graphically. The reflex association of the contractions with swallowing was established and the production of inhibition by reflex and drug actions was studied. Phillipson (185) has studied the flow of digesta from the abomasum of sheep by collecting it from a cannula which diverted the flow outside the body. Between feedings the digesta flowed in gushes into the duodenum. Quiescent periods of 15 to 30 min. sometimes occurred, although during rumination flow was most regular. Feeding usually caused temporary brief interruptions of flow from the stomach. Inflation of a small balloon in the duodenum reduced the out-

put from the abomasum. Continuous collections indicated that normally digesta passed from the stomach to the duodenum during about 17 of each 24 hr.

The rate of passage of a barium meal through the digestive tract of two pony foals has been tested by Alexander & Benzie (186). The stomach emptied in 4½ to 5 hr. when the foals were in the suckling age, and in a shorter time after they were weaned. Barium reached the colon in 1 to 3 hr. and was excreted in 24 to 48 hr. Balloons were passed via the nasopharynx into the stomach of trained unanesthetized ponies by Alexander (187). In the fasted state he found the usually quiescent state of the stomach was interrupted by bursts of large hunger-type contractions (type II), the rate of which was 3 to 8 per min. With feeding, type II contractions were often induced but ceased shortly after feeding was completed. Administration of epinephrine caused a brief (minutes) period of inhibition while atropine produced prolonged (hours) inhibition. Isolated strips of the wall of the stomach of horses showed strong slow rhythmic contractions when suspended in Tyrode's solution (187). Strips from the pyloric end contracted more rapidly than did those from the body of the stomach.

In the study by Masson & Phillipson (181), the concentration of volatile fatty acid in the material entering the duodenum was one seventh (or less) of that of the ruminal contents indicating, in confirmation of earlier work, that short chain fatty acids formed in the rumen are mainly absorbed before they reach the small intestine. Some indirect evidence was obtained, suggesting that water was absorbed before the food enters the abomasum, presumably in the omasum.

Actions of Drugs

Various drug actions on secretion are discussed in the following papers: (56, 62, 64, 65, 188, 189); the actions of drugs on gastrointestinal motility are discussed (190 to 195).

Experimental Pathology

Experimental Ulceration.—By means of acute perfusion experiments in cats, and chronic, diverting surgical procedures in dogs, the pronounced susceptibility of the esophagus to bile, pancreatic juice, and mixtures of these was demonstrated by Cross & Wangensteen (196). Resection of the upper half of the stomach and terminal 1 cm. of the esophagus combined with vagotomy and esophagogastrostomy in dogs was found by Kiriluk & Merendino (197) to be followed by severe ulceration in the esophagus in one third of the animals. Vomiting also was usually present; it may have been due to the vagotomy. It certainly would contribute to the regurgitation of acid-peptic material from the stomach into the esophagus. In dogs, transplantation of the antrum into the transverse colon was found by Dragstedt, Oberhelman & Smith (198) to be followed by ulceration in vagotomized pouches of the entire stomach, by gastrojejunal ulcers when the stomach was

united with the jejunum, and by no ulcers when the stomach was reunited with the duodenum. Cross, Ferguson & Wangensteen (199) undertook to determine how much of the acid-bearing part of the stomach in dogs must be removed to protect the animals against ulceration provoked by histamine in beeswax, when the antrum is left intact and in continuity with the remaining portion of the stomach and with the duodenum. No ulcers developed when only 10 per cent of the stomach by weight was left as the residual acid secretory part, while ulcers did occur when the acid secretory remnant represented 25 per cent or more of the total weight of the stomach.

In an ingenious series of experiments by Toon, Cross & Wangensteen (200), dogs smoked cigarettes through permanent tracheal stomas fitted with cigarette-holder T tubes. The daily inhalation of the smoke from five cigarettes did not provoke formation of peptic ulcers or any other detectable changes. The cigarette smoke likewise did not stimulate gastric secretion in dogs with pouches of the entire stomach. There was some indication that five to ten cigarettes a day increased temporarily the ulcerogenic effect of histamine in beeswax although even in these animals the development of ulceration was not more rapid than in some other control series of animals studied previously in the laboratory. Ingle, Prestrud & Nezamis (201) found ulcers in the pyloric portion of the stomach in 21 of 36 rats which had received cortisone daily in varying doses for periods up to 21 days. The lesions ranged from multiple tiny ulcers and shallow erosions to a few deep bleeding ulcers.

Williams (202) produced erosions in the stomach and duodenum of guinea pigs in a very short period, sometimes within 4 hr., by the injection of 2 to 12 mg. of histamine in beeswax mixture. In a further analysis of the cause of the increased susceptibility of guinea pigs to histamine-induced ulceration following thyroidectomy, Watman & Nasset (203) showed that restoration of a normal basal metabolic rate by pure thyroxine or diiodotyrosine still leaves the animals more susceptible to ulceration. Use of whole desiccated gland, however, restored both the basal metabolic rate and the susceptibility to ulceration to normal. The results indicated a gastric factor in the thyroid gland of the guinea pigs which was independent of the calorigenic function of the gland and which in an unknown fashion affected the susceptibility of the mucosa to ulceration by histamine.

The technique of duodenal ligation is being used widely in tests of ulcerogenic and antiulcer factors. Funk *et al.* (204) presented data indicating that the occurrence of hematuria or pigmentation of the urine during an 8-hr. postduodenal-ligation period is associated with reduced incidence of ulceration in the stomach of rats. When ulcers were present in the stomach, ulcerations and perforations were also seen in the esophagus of nearly half of their animals. The variability in the occurrence of gastric ulceration may have been due to differing nutritional status in the various batches of animals they used. Alexander & Merendino (205) have confirmed the finding that vagotomy affords complete protection against ulceration following duodenal ligation in rats. In addition, when they demonstrated that placing artificial

gastric juice in the stomach after duodenal ligation in vagotomized animals results in the same, or nearly the same, ulceration as occurred spontaneously in intact rats after duodenal ligation, they were able to conclude that depression of secretion after vagotomy was the major mechanism of the protection.

The chlorohydrate of diethylaminoethyl-N-dibenzopara thiazine (Diparcol; 2987 R.P.), a cholinergic blocking agent, used sometimes clinically in the treatment of parkinsonism, when given by Kowalewski and co-workers (206) to rats before duodenal ligation, reduced the acidity and volume of the juice and the frequency and severity of ulceration.

In tests by Funk *et al.* (207) the oral, subcutaneous, or intraperitoneal administration of acid potassium acetate prepared from the nonprotein fraction of extracts of gastric mucosa completely prevented the occurrence of ulceration in rats with the pylorus ligated for 8 to 9 hr. When this was found to be the active ingredient of such extracts other salts were tested; the most potent salts were potassium acetate and sodium acid acetate. A possibly related, but completely independent, observation was made by Küng (208) when he demonstrated that the administration of a protein-free extract of stomach and duodenum (Robuden) to rats reduced the ulceration occurring after duodenal ligation. It seems possible that acid potassium acetate is also the active ingredient in Robuden. The daily installation of crystalline lysozyme into blind ileocolic pouches in dogs for periods up to 162 days by Moeller, Klotz & Kirsner (209) failed to produce gross or microscopic changes in the bowel even when the concentration of lysozyme was maintained at 20 times that usually encountered in patients with ulcerative colitis. These results, like those of others, were interpreted to indicate that lysozyme is not of primary etiologic significance in ulcerative colitis.

Experimental Obstruction.—The motility in Thiry-Vella fistulas of the lower portion of the ileum of dogs was reduced for 3 to 15 days after high intestinal obstruction in an experimental study by Gazes, Richardson & Cotten (210). By then, muscular weakness, dehydration, and lethargy had developed. The intravenous infusion of isotonic potassium chloride at this stage produced a prompt increase in motility. Both the small rhythmic waves (type I) and peristaltic movements (type III) were stimulated. Similar amounts of potassium chloride given to normal dogs had no effect on motility.

Clarke *et al.* (211) have tested some factors that influence loss of salt and water in dogs with pyloric obstruction. Replacement of fluid loss by parenteral administration of 5 per cent solution of glucose after the obstruction had been produced, or resection of the antrum before the obstruction, were the only two procedures of nine tested which prolonged the lives of the dogs with obstructed pylorus. Lans, Stein & Meyer (212) have suggested that the success of the glucose solution may rest in providing sufficient water for maximal adjustments to the abnormal and unbalanced losses produced by the obstruction. Giving water *ad libitum* by mouth to the dogs increased the losses of fluid and chloride and shortened the survival time. Physiologic

saline solution *ad libitum* in place of the drinking water reduced the losses of water and chloride in the vomitus but shortened survival to the same extent as water alone by mouth. Saline solution by clysis or vagotomy likewise did not help the dogs. The results are difficult to interpret, possibly because determinations of total losses of important electrolytes were not included. The lifesaving effects of the administration of potassium to patients under similar circumstances (212) suggest that loss of this ion may also have been an important factor in the dogs. As pointed out by others and emphasized in these studies (211, 212), replacement therapy in such states, whether produced experimentally or by disease, is complex and cannot be accomplished by such a simple fluid as 0.9 per cent solution of sodium chloride.

Light (213) has advanced evidence indicating that lysozyme is present in the contents of obstructed loops of small bowel of dogs, and that it accounts for at least some of the toxicity of alcoholic precipitates of such material. No lysozyme was found in the contents of the small bowel of normal dogs.

Experimental Pancreatitis.—Rush & Cliffton (214) show pancreatitis caused by ligation or injection of the ducts with bile to be associated with a rise in proteolytic activity in serum, a fall in antiproteolytic titer in serum, and a fall in arterial pressure. These changes were temporarily reversed in three dogs by the intravenous injection of soybean tryptic inhibitor. A rise in concentration of serum amylase was observed whenever the pancreatic ducts were ligated or injected under presssure in studies by Persky *et al.* (215) and by Thistlethwaite & Hill (216). The rise in value for serum amylase and the destructive changes in the gland following ligation of the ducts were found by Schaffarzick, Ferran & McCleery (217) to be reduced when vagotomy was performed prior to the ligation of the ducts. A similar result was obtained by Shingleton, Anlyan & David (218) when methantheline was given to dogs which had ligated ducts but methantheline had much less effect on the pancreatitis produced by injection of the ducts with bile under pressure. Successful use of the drug in the treatment of three patients who had acute pancreatitis has been reported by Shingleton & Anlyan (219).

Oral administration of aureomycin before or immediately after injection of the ducts with bile caused a dramatic improvement in the survival rate of the animals studied by Persky and co-workers (220). Without treatment most of the animals died; when given aureomycin all survived. The authors present evidence indicating that the action of the antibiotic was chiefly directed against the anaerobe clostridia which were found in great numbers in the liver and pancreas of animals which succumbed to the pancreatitis. In the light of other evidence on the mechanism of the pancreatitis and the death of the animals, a search for possible effects of aureomycin or proteolytic enzymes in the serum seems indicated.

The production of pancreatitis by ethionine, the ethyl analog of methionine, has been extended by de Almeida & Grossman (221) from rats to include dogs, cats, and monkeys. Their study indicates that the effect of ethionine is directly on the acinar cells leading to eventual dissolution. Accom-

panying this process there was reduced pancreatic secretion in response to stimulation by secretin and eventually a rise in the concentration of serum amylase and lipase. Degenerative changes in acinar tissue followed by extensive pancreatic fibrosis was observed by Miller & Rigdon (222) in ducklings fed purified diets in which sucrose or dextrose was substituted for cornstarch. No changes were noted in the islet tissue. The degenerative changes developed rapidly, indicating, in ducklings at least, a rather pronounced susceptibility of the acinar tissue to dietary factors.

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THE INNERVATION OF SKELETAL MUSCLE

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This review is limited to a discussion of recent advances in studies of the nervous supply of skeletal muscle. It is divided into the following sections: (*a*) a short list of some recent symposia which will afford the reader reference to a more extended field than that covered by this article, (*b*) afferent, and (*c*) efferent supply, and (*d*) the electromyogram. Most of the material of section *d* will deal with action potentials from human muscles, both in the normal individual and in patients suffering from a variety of neural or muscular diseases.

Neglect or cursory treatment of electromyography in previous volumes of this series is a result of the limitations of space imposed on writers whose interests lie in other special aspects of muscle physiology where the overpowering wealth of new material demands critical survey. In addition, however, there does appear on the part of some physiologists the remarkably naïve assumption that human physiology is not "basic" and is to be ignored or treated with deference and pity, to be relegated to clinical lore or to journals of "applied" physiology—a lesser breed. Such an attitude perhaps reflects our restricted training which induces us towards the grasping of techniques and away from reflections on the broader implications or applications of facts compiled by means of our exquisite craftsmanship.

The contributions of medicine and other "applied" sciences to physiology are common knowledge and need not be emphasized here, but inclinations to subdivide physiology away from medicine can only be deplored. DuBois (1), from the vantage point of long and valuable service in many branches of physiology puts the case succinctly, thus:

> Physiology has no limitations in any discipline that deals with living matter. The more that physiology invades anatomy, clinical medicine, and all other departments, the better it becomes for science as a whole. It is not the title that makes the physiologist, it is the point of view, the mode of thought.

General

The proceedings of several symposia of general interest to muscle physiologists are now available. A conference under the auspices of the *Centre National de la Recherche Scientifique* which took place in 1949 has been published in the *Archives des Sciences Physiologiques* (2). Although much of the conference dealt with the recent work of expert axonologists and synaptologists, there is enough material concerning the general features of biological membranes, including muscle, drug action, problems of neuromuscular transmission, and muscle innervation to recommend the findings presented even to those with strictly "muscular" interests. It would appear

to this reviewer that the transactions would have achieved more easily the wide circulation they deserve had they been published as a monograph instead of in the pages of a relatively new journal.

A colloquium on muscle was sponsored by the World Health Organization and UNESCO in France in 1950 (3). This conference was heavily weighted toward the biochemical aspects of muscle, but several meritorious papers concerned with normal innervation, denervation, mechanics, and pathophysiological considerations are included. The Brussels conference of June, 1951 was concerned with mechanisms of synaptic transmission (4). The symposium on curare of the New York Academy of Sciences (5) should be of great interest to all those involved in pharmacodynamic research.

At the time this review was written, neither the transactions of the Ciba Foundation's February, 1952, conference on the spinal cord (6) nor the symposium on "The Neuron" held at Cold Spring Harbor in June, 1952, had yet been published. The quality of the contributors and the scope of the topics covered make it certain that the contents of both of these volumes will be highly rewarding.

Muscle Afferents

Recent histological investigation of muscle afferents has added some detail to what was already known from Sherrington's (7) earlier studies. Rexed & Therman (8) examined the nerve fiber distributions to flexors and extensors. Almost simultaneously Lloyd & Chang (9) presented much more complete studies of the afferents from 16 flexors and extensors of the femoral and crural muscle groups in the cat. They found that in the demotored nerves of all muscles examined there were three groups with fiber diameter peaks at roughly 15 to 17 μ, 6 to 7 μ, and 3 μ. Their size grouping suggests their probable physiological function as participants in the various muscle to muscle reflexes [see Lloyd's chapter 4 in Fulton's text (10) for a summary of these reflexes]. Lloyd & Chang (9) showed also that nerves from extensors contain larger fibers than the nerves from flexors and that the proximal (femoral) musculature was innervated by larger afferents than the distal (crural) muscles. The latter observation is in keeping with the general thesis on the size of efferents to proximal and distal muscles discussed below.

Barker's (11) major concern, in an excellent paper, is the detailed histology of the muscle spindle, and additional pertinent information regarding the large size of afferents from these organs is given.

Szentágothai (12) destroyed dorsal root ganglia and five to eight days later found degenerating boutons on motor horn cells, thus providing anatomical evidence for the monosynaptic reflex. He thought that the large degenerated fibers found in the muscle spindles constituted part of the afferent limb of the two-neuron arc. In addition, Szentágothai suggests that medium-sized fibers of the spindle are also connected directly the the motoneuron. The latter does not correspond with Lloyd's (10) insistence on the exclusive participation of the largest afferents in the two-neuron arc.

Much of the recent physiological work on muscle afferents is a by-product

of attempts to study in greater detail the reflex rôle of various sensory fibers, particularly those which influence the two-neuron arc. Since much of this material has already been analyzed by Brooks & Fuortes (13), and will be discussed in addition in other sections of this volume, it will be treated with considerable brevity here. The new material on muscle afferents is of main interest in this chapter.

Eccles and co-workers (14) recorded several humps in the compounds action potential picked up from dorsal roots on stimulation of a muscle nerve (and vice-versa) and studied the effects of stimulation of various afferents (15). Their results substantiate the histological findings of Lloyd & Chang (9). These workers, however, would suggest a refinement of group II fibers into two subgroups on the basis of conduction velocity. Brock, Eccles & Rall (14) point out the difficulty of activating significant numbers of group I fibers alone without bringing in some of the larger afferents of group II. This point is also noted in Magladery and co-workers' electrophysiological studies of normal human reflex patterns (16, 17). Taken in conjunction with Szentágothai's (12) histological data, these observations may help to resolve the discrepant findings of the reflex consequences of afferent stimulation that now plague several groups of investigators.

It is now generally held that the largest afferents in a muscle nerve (the group I fibers) come from the annulo-spiral endings of spindles [A endings of Matthews (18)] as well as from the Golgi tendon organs (B endings) [Lloyd (19); Granit (20); Hunt & Kuffler (21, 22, 23)]. It is not possible, however, to separate out these two kinds of fibers of diverse origin and function by action potential recordings (14). The prevailing opinion seems to be that the fibers from spindles are generally somewhat the larger of the two.

The question of whether group I fibers can exert inhibitory influences on the motoneurons supplying the muscle from which the afferents originate is the subject of lively current discussion. Granit's (20) contention that such "autogentic" inhibition occurs (following an initial facilitatory influence) is supported by his colleagues Hagbarth & Naess (24, 25) and is also suggested by McCouch *et al.* (26). Lloyd (27, 28), on the other hand, does not believe that these afferents are autogenetic inhibitors or inhibitors to synergistic muscles, but only excitatory. Brock, Eccles & Rall (14) and Eccles & Rall (15) are in agreement with Lloyd on this point. Magladery's (16, 17, 29) studies on human subjects would support the views of either of the two schools of thought since his depression of monosynaptic reflex response could be ascribed to the activation of the largest afferent fibers or to the presence in addition of some group II discharges in the centripetal volley. As has already been noted (14), such compound activation is quite likely in any electrical stimulation of an afferent trunk from muscle.

Muscle Efferents. Small Nerve Systems

An important advance in our understanding of the mechanisms of control of muscular contraction has been the recent clarification of the rôle of the small nerve fibers which leave the spinal cord by way of the ventral roots

and make their way in the mixed nerve trunks to end in skeletal muscle. Eccles & Sherrington (30) demonstrated by classical histological methods that a nerve to a muscle (e.g., gastrocnemius) deprived of its afferents contained a large number of fibers in the 3 to 8 μ range (about 30 per cent of the efferents), as well as the heavily myelinated large fibers ranging in diameter from 8 to about 18 μ. A similar sizeable group of small efferent nerve fibers was discovered in frog muscle. The tacit assumption had been that these small fibers to muscle were similar to their coarser fellows in the ventral roots and that they were quantitatively different only and innervated smaller motor units. Recent material has presented significant qualitative functional distinctions between the small and the large nerve fibers to skeletal muscle, in both amphibian and mammal.

Amphibian.—Tasaki & Mizutani (31) showed that the small nerve fibers to frog muscle evoked slow contractions, quite at variance with the rapid twitch response which ordinarily results from stimulation of vertebrate motor nerves. By dissecting the small fibers away from the large axons running along with them in the muscular twig, or by selectively blocking conduction in the large fibers by a constant current, Kuffler & Gerard (32) could study the properties and functions of the small fibers without interference from the coarser efferents. They confirmed the earlier finding that excitation of the small nerves produced slow contractions and further showed that the responses were nonpropagated local contractions, limited to the region of the neuromuscular junction. Accompanying the localized contraction was the small junctional potential, which resembled the decrementing, electrotonic endplate potential of curarized vertebrate or normal crustacean muscle. Threshold was considerably higher and conduction velocity less in the small fibers, in agreement with expectations from studies relating these properties to fiber diameter (33, 34). Tension produced by localized contraction could be graded and was found in some cases to be as much as 15 per cent of that obtainable from a maximal twitch.

Further analysis (35) showed that the small fibers could be aroused reflexly without activating the large fibers which supply the muscle elements yielding the all-or-none contraction and its associated propagated spike potential. The possibility that a single muscle fiber might be innervated by both a large and a small nerve fiber was left open by Kuffler and his coworkers (32, 35). It now appears (36) that frog muscle does not receive this type of dual innervation, thus differing from the frequent occurrence of multiple nerve supply of muscle fibers of crustaceans, insects and other invertebrates [Prosser (37)].

Katz (38) believed that the small nerve system might innervate the intrafusal fibers of the frog's muscle spindle (as has been shown in the mammal, see below). His re-examination of this system, however, indicated clearly that these nerves were not a specific part of the spindle system.

On the basis of the work cited, it was suggested by Kuffler (32, 35) that the frog's small nerve-muscle system performs the task of maintaining vari-

able small amounts of tension over extended periods of time. It would appear that such "tonic" activity is carried out more economically in this way than by the motor unit twitches utilized by mammalian forms for a similar purpose [cf. Prosser (37) for a brief discussion of this point).

Insofar as its small nerve supply is concerned, the mechanical comportment of frog muscle thus resembles the response most commonly noted in crustaceans: namely, the local contraction of the "slow" system [Katz & Kuffler (39); Wiersma (40, 41)]. A major distinction between these muscles, however, lies in the fact that the end plate potential and local contraction of the crustaceans can be facilitated to yield a propagated spike potential and rapid twitch. This is accomplished by applying the proper number and frequency of stimulation to the "slow" nerve. Such an effect can not be obtained by exciting the frog's small nerve efferents, only the large motor axons being capable of producing the twitch.

If the suggestion is entertained that local contraction represents the basic contractile response [Wiersma (41)] and the twitch a specialization which has been extensively utilized chiefly by vertebrates, the frog would represent an interesting intermediate between primitive and highly complex organisms. For, whereas local contraction appears to be the prime reply to motor nerve bombardment in the crustaceans, the twitch is the universal response of the tension-producing elements of the mammal. Although some crustacean muscles respond with the rapid twitch to indirect stimulation ("fast" systems), others ("slow") give either local contraction or propagated twitch (see above). Specialization has apparently proceeded in the frog to the point where one ensemble of nerve neuro-muscular junction and muscle fiber will produce only localized contraction, whereas the second system responds with the propagated contraction. In the mammal, the only contractile response which yields tension or movement is the twitch. Only under unusual conditions such as denervation, partial damage, etc. will local contracture take place in mammalian striated muscle. Perhaps this reaction is one of the remaining echoes of its fundamental evolutionary heritage.

It is interesting that long-lasting acetylcholine and KCl contractures were obtained from that portion of the iliofibularis muscle of the frog which is supplied by small motor nerves ("slow" portion of the muscle). The "fast" part of the muscle (innervated by large motor axons) produced minor contractures lasting for only a few minutes when immersed in solutions of the same agents [Kuffler (36)]. Whether or not future work shows this correlation to be of general application, it is already apparent that studies of contracture and drug action on muscle should be reinvestigated in the light of recent data which have so clearly shown the presence of distinctive types of innervation and contractile responses of vertebrate muscle.

Mammalian.—The ideas of Eccles & Sherrington (30) on the function of small nerve fibers in mammalian ventral roots (p. 142) were brought into question by the work of O'Leary, Heinbecker, & Bishop (42). They showed that stimulation of these nerves did not add an appreciable increment of

tension to that produced by exciting the large fibers and suggested that the small fibers innervated the intrafusal elements of the muscle spindle. Such a hypothesis appeared logical on the basis of histological evidence showing that the spindles received a somatic motor supply [Hinsey (43, 44); Barker (11)]. Haägqvist (45) and later Tasaki & Tsukagoshi (46), however, felt that the small nerve fibers regulated muscular "tone" in the mammal and that their over-response lay at the basis of spasticity. Leksell (47) produced clear physiological evidence against Haägqvist's views and demonstrated the correctness of the surmise that the small nerve fibers constituted the motor innervation of the muscle spindle. He recorded a "tail" to the spike potential recorded from the ventral root when a muscular twig was stimulated and proved that the "tail" was due to irritation of high threshold fibers ("gamma" efferents) whose diameters clustered around 5 to 6 μ in accordance with the known diameter spectrum of the particular muscle nerves studied. Stimulation of the "gamma" fibers produced negligible muscle tension but did arouse an outburst of afferent discharge from the muscle's stretch receptors.

Leksell's work was followed by a series of brillant papers by Kuffler & Hunt (21, 22, 23, 48) which have clarified to a remarkable degree efferent control of the spindle, the afferent consequences that follow the activation of the small motor nerves and the importance of spindle regulations in reflex muscular adjustments.

Stimulation of the small motor nerves (3 to 8 μ) in the ventral roots did not develop tension but did yield small potential changes which could be recorded in thin muscles such as the tenuissimus. These potentials were thought to be derived from the response of the intrafusal muscle fibers of the spindle. The efficacy of small nerve stimulation was enhanced when the muscle was under stretch and reduced when it was slack [Kuffler, Hunt & Quilliam (48)].

The work of Kuffler and co-workers is neatly correlated with Matthews' (18) studies of twenty years ago. The latter showed that two groups of stretch receptors could be distinguished in muscle: those whose discharge was reduced during contraction (A type, from spindles) and those whose activity was increased during muscular contraction (B type, from tendon organs). Kuffler & Hunt (21, 22, 23, 48) demonstrated that the activity of A endings only was influenced (increased) by stimulation of the small nerve fibers. They proved also that muscle stretch and small nerve stimulation were synergistic so far as the afferent outflow from A endings was concerned. Thus the reduction of information from the periphery which would accompany the isotonic contraction of a muscle (i.e., by reduction of stretch on spindles) can be compensated by an increased contraction of the intrafusal fibers of the spindle due to an increased outflow over the small efferents. The small nerve system thus seems adapted to act as a peripheral regulator of spindle action.

That the afferent discharge to the spindles may function normally to compensate for variations in muscle length is indicated by the fact that

during reflex action small motor nerve activity increases concomitantly with the excitation of the large fibers evoking contraction [Hunt (49)]. The "gamma" fibers have been shown to be tonically active, even during "rest" of the muscle [Hunt (49); Granit & Strøm (50)]. These fibers thus appear to keep the spindles at a level of tension close to that needed for firing the afferents.

Extraordinarily fine gradations in spindle discharge (and all this implies for reflex action) could conceivably be achieved by the mammal, as indicated by the following considerations: (*a*) approximately one third of all the fibers of a lumbosacral ventral root are devoted to spindle innervation, (*b*) each spindle is supplied by more than one nerve fiber, and each small fiber serves more than one spindle (11, 22); (*c*) variable effects on spindle discharge can be produced by interaction of the separate efferents or by stimulation of a single efferent at different muscle lengths [Kuffler & Hunt (21); Hunt & Kuffler (22)]; (*d*) sub-threshold effects of the stimulation of one fiber may be summed with the response to excitation of a neighboring fiber (21, 22, 23).

In addition to the peripheral and spinal mechanisms so clearly shown to be concerned with muscle spindle regulation, recent evidence of a supraspinal organization involving these end organs has been given by Granit & Kaada (51). These workers showed facilitation and inhibition of spindle discharge and "gamma" fiber activity as a result of stimulation of regions of the brain stem which enhance or suppress the vigor of muscular contraction. It is certainly to be anticipated that many other levels of the neuraxis will also be shown to be capable of exerting diverse effects on this system.

Although the important finding that small nerve fibers going to mammalian skeletal muscle supply muscle spindles is beyond peradventure, it is worth injecting a note of caution at this point. Kuffler & Hunt (21) state that "all small nerve fibers in the lumbosacral outflow of the cat appear to innervate muscle spindles" and further thant "small nerve fibers innervate muscle spindles exclusively." Such a generalization appears unwarranted, for Hodes *et al.* (52, 53) have found that the largest axons to some of the small muscles of the human foot have a conduction velocity of around 50 m./sec. and hence would be about 8 μ in diameter, clearly in the size range of "small nerve" efferents. Some human extrafusal muscle fibers must be supplied by nerves as small as 5 μ, for a conduction rate of 29 m./sec. in nerves to one of the small foot muscles has been reported (53). The cat probably does not differ significantly from man with regard to the nervous control of the distal musculature, for conduction rates in the motor nerves supplying the latter have been found (54) to be considerably less than velocities attainable from the nerves to larger, more proximal muscles (e.g., quadriceps, tibialis anticus, and gastrocnemius). Thus, it would seem that the extrafusal fibers of small muscles may be innervated by nerves of about the same diameter as those which go to intrafusal muscular elements in the large fleshy muscles. Even in large muscles, the separation into large (to extrafusal fibers) and small (to intrafusal fibers) nerves is not rigid, and some

overlapping occurs. For instance, Leksell (47) was not always able to separate by threshold stimulations the smallest alpha fibers (which produce tension) from the largest gamma axons.

Whether the small motor fibers which go to small distal muscles actually supply smaller motor units than those to large muscles [Eccles & Sherrington (30)] or whether their small size can be related to some other physiological or anatomical distinction between the muscles, must await future work. Also of some interest would be a study of the size of the fibers distributed to the muscle spindles of small muscles. One would expect that these end organs should be cared for by axons smaller than those supplying extrafusal elements, that is, probably by fibers less than 5 μ in diameter.

Summary.—Because there appears to be a striking anatomical homology in the two types of fiber (small and large) distributed to the skeletal muscles of amphibian and mammal, one might have expected functional similarities as well in the two efferent nerve systems. Yet the small motor fibers play no direct part in the production of tension in the mammal. In the frog, on the other hand, they are of considerable importance in the maintenance of a slow local muscular contraction which may be aroused either by small nerve stimulation (32) or, what is of great significance from the standpoint of the functional organization of the motive system, can be aroused reflexly (35).

And yet, certain similarities do appear to exist between the small nerve systems of the two species. In both, the small nerve systems are much more resistant to fatigue than the elements responsible for the quick twitch. These fibers are frequently seen to be active when those fibers which produce rapid phasic movements are quiescent. Acetylcholine will activate the neuromuscular junctions of the small nerve systems and curare will block the action of this drug. Acetylcholine stimulation is manifested by the production of tension in the frog and by an outburst of potentials from the spindle afferents in the mammal [Kuffler (36)]. In neither species are the muscle fibers supplied by large axons thrown into action by acetylcholine. Kuffler *et al.* (48) believe that local contraction of the mammalian intrafusal muscle fibers occurs, thus pointing to further basic similarities between frog and cat. Because of technical difficulties it has not been possible to test directly the suggestion that the fibers within the end organ react by a nonpropagated local contraction. But the fact that the afferent discharge can be graded as a result of facilitation of small nerve effects would appear to be strong presumptive evidence in favor of this view.

One is thus left with the impression that the different end results of activation of the small nerve system in the two forms is due to distinctive intraspinal and supraspinal types of organization rather than to fundamentally diverse modes of peripheral response. The emphasis on speed of action and precise regulation of fine muscular adjustments has been met in the mammal by the exclusive use of the propagated twitch reaction. The maintenance of small, long-lasting tension is accomplished by alternation of activity of dif-

ferent motor units within the muscle mass rather than, as in the frog, by the continuous utilization of the efficient local contraction evoked by small nerve action.

Muscle to (35) muscle reflexes appear to have advanced to a dominating position in the regulation of both tonic and phasic responses in the mammal, whereas the origin and control of much reflex activity appears to reside in the skin in the frog. The stretch receptor itself has become of such supreme importance to the bodily requirements of the mammal, in posture, locomotion, flight, etc., that the central organization has provided means for its intricate efferent control as well as abundant pathways for receiving from it more and more complicated signals as to its functional state. This in turn results in a regulated efferent output to the end organ.

From what has been said of the different types of muscular reactions available, the importance of species distinctions and the need to limit generalizations concerning muscular mechanisms are apparent. The frequent and often unjustified retreat of embattled disputants into the safe sanctuary of "species differences" as an excuse for failure to re-examine data or revise theories, appears to have some validity in the case of studies of muscle action.

Knowledge about the muscle spindle has steadily increased since Sherrington (55) and Ruffini (56) described the organ, and Sherrington's classical work emphasized its importance in the regulation of reflex action (57). Fulton's (58, 59) examination of myotatic reflexes, Matthews' (18) classification of afferent muscular discharge, and Lloyd's (10) superb electrophysiological analyses of monosynaptic reflexes have all added significant information for the synthesis of current concepts. Interest in muscle spindle innervation remains keen, and Barker's (11) paper has organized much of the histological material into conformity with physiological thought. His discussion of the means by which mechanical input to the intrafusal muscle fibers may be translated into the electrical output in the afferent fibers seems unnecessarily involved, however, and it is gratifying to note the initial experimental approaches to this problem recently undertaken by Katz (60, 61).

Some of the developments outlined in the preceding pages appear to have placed within view a fairly sophisticated outlook on the anatomical complexities and organization of the physiological refinements of muscle function. In the light of recent advances, it would not be amiss here to suggest that some of our concepts of muscle disease might well be re-examined. One can readily concur with Couteaux (62) that

> It is indispensable for the complete definition of a muscle innervation, to characterize not only nerve fibers, structurally and functionally, the type of nerve ending, the type of junctional potential and the type of muscular response elicited, but also the particularity of structure and chemical activity of the juxtatermination. Histological and histochemical research in this specialized zone of muscle is now a prerequisite in the study of muscle pathology, since this highly differentiated area seems to be able to intervene directly in the constitution of diverse neuro-muscular syndromes.

ELECTROMYOGRAPHY

The work cited in this section is purposely not confined to the one- or two-year period generally covered in reviews of this series. Nor will there be any attempt at meticulous thoroughness. For it is felt to be more pertinent to try to give an account of the major developments rather than mere serial cataloguing or sentence summaries of papers on many diverse subjects about which significant generalizations can not be made at this time.

Many papers published prior to 1949, not discussed in this section, are listed in the last two pages of Sandow's review (63). Also some of the work published during the war and early post-war years are summarized in the section on electromyography by Buchthal (64). In addition several other reviews and symposium articles will give the reader a more complete bibliography (65 to 76).

Methods.—With the advent of adequate instrumentation, serious investigation of the human electromyogram was undertaken by Piper (77), who stimulated nerves and recorded muscle action potentials by surface electrodes placed on the skin overlying the activated muscles. Hoffman (78) examined the response of muscles to direct stimulation of motor nerves. He also examined the reflex responses which occurred when a mixed nerve was activated percutaneously. As has been recently emphasized by Magladery & McDougal (79), Hoffman's deductions on the similarity of his reflex to the stretch response, on the rapid conduction of the afferents, and on the short central delay were extremely prescient.

Adrian & Bronk's (80) technique of recording from single motor units by means of small concentric electrodes thrust into the intact muscle was quickly and extensively utilized in electromyographic studies of normal and abnormal muscle (as, e.g., 81 to 86). Whereas the nerve stimulation-muscle recording method is most useful in studies requiring accurate timing as in conduction velocity (52, 53, 79, 87), neuromuscular junction (88 to 99), or reflex studies (16, 17, 29, 79, 100, 101, 102), it suffers from the serious limitation that such simultaneous motoneuron activation is not the normal mode of function of neural and muscular elements.

The form of the unit potential is generally simpler than that derived from surface recording over the muscle activated by maximal motor nerve stimulation. This is true not only because of the artefacts introduced by the recording method (103), but also because the action potential from a whole muscle represents the resultant of an unresolvable complex of a large number of unit potentials differing in time of onset, in duration, in amplitude, and occasionally also in form (104, 105, 106). Thus, the simplicity of the unit potential recommends its use, especially in many studies where the form of the potential is important in the detection of abnormal innervation as, e.g., in cases of peripheral nerve injuries, neuritides, or old age [Weddell *et al.* (104); Buchthal (70, 107, 108); Kugelberg & Petersén (109, 110, 111); Denny-Brown & Pennybacker (85)]. It is thus apparent that a combination of the nerve stimulation method and the voluntary activation of motor units

is desirable for the most complete description of neuromuscular functioning.

With the onset of World War II interest in human neuromuscular disorders increased considerably. Much of the work was aimed at assessing the extent of nerve damage resulting from various types of trauma and at devising methods which might be more accurate than the clinical examination for determining whether the injured nerve was recovering spontaneously (and hence would usually not be operated) or whether its progress after surgical repair was satisfactory. Though it is generally agreed that the practical contributions of electromyographic research to prognosis and diagnosis were disappointing, a marked upsurge of basic data as well as improvements both in technique and apparatus did result [cf., e.g., Lambert (112) and Sandow (63) for technological advances].

Form of the action potential.—In the course of their work on traumatic nerve injuries Hodes, Larrabee & German (52) described the form of the muscle action potentials obtained from the major muscle groups of the human arm, leg, hand, and foot. Whereas the small hand and foot muscles generally gave simple diphasic potentials upon maximal stimulation of their motor nerves, the larger muscles of the extremities were very complicated, with evidence of two or three, or occasionally more, potential crests. As the recording electrodes were moved over various portions of the active muscle, a particular peak would grow in prominence and then recede as another grew with further shifting of the electrodes.

The complicated form of the potential noted above was in keeping with and partly explainable by the important work of Eccles & O'Connor (113) who studied the electromyogram obtained from stimulation of the "cut-down" motor nerve to soleus and a few other muscles. These workers found that the only condition in which a simple diphasic response occurred was when the recording electrodes were over a rather narrow region containing the end plates. They thus assumed that the activity was recorded close to its origin (region of the end plates) in this case, whereas the various positive and negative peaks picked up under other recording conditions were due to conduction of the brief wave of negativity along muscle fibers embedded in a conducting medium [Bishop (114); Lorente de Nó (115)].

On the basis of the work of Eccles & O'Connor (113), one would assume that the end plates are localized in a relatively small area of the hand and foot muscles, whereas their distributions are widespread throughout the larger muscles. Temporal dispersion due to conduction over motor axons of widely different diameters probably does not introduce significant complexities of form into the action potentials recorded in the usual human electromyogram. For, conduction velocity in the nerve trunk supplying the short toe flexors of the foot range from 29 to 54 meters per sec. [Hodes (53)], and no significant divergence from diphasicity is usually found in this group. Whether temporal dispersion due to varying conduction distances or velocities over the fine intramuscular twigs does in fact contribute to the intricate potential pattern of larger muscles, cannot be answered at this time.

An outstanding contribution to the understanding of the shape of the electromyogram is contained in the recent paper of Jarcho *et al.* (116). The anterior gracilis muscle of the rat was chosen because it is superficially placed and anatomically simple (being small and consisting largely of parallel fibers). Jarcho stimulated the nerve twig supplying the anterior gracilis and systematically moved recording electrodes over the entire length and breadth of the muscle in millimeter steps. The muscle potential maps thus obtained showed potentials which were roughly diphasic in form and were followed by a second diphasic wave which was usually smaller, broader, and had a tendency to show secondary peaks. The initial diphasic potential did not have the same direction in all records and was seen to reverse at two sharply localized regions of the muscle. The reversal zones corresponded exactly with the region where end plates were concentrated. This was conclusively shown by subsequent histological control and also by the fact that when the muscle was curarized the end plate potential was obtained from these two regions only. The first-spike was considered to be due to the negativity arising from end plate regions nearest the recording electrodes. The later waves resulted from activity conducted from the distant end plate regions. When the twig innervating the distal end plates was severed, stimulation of the nerve now caused a change from the original complex potential wave to a simple diphasic response. It is reasonable to expect the late wave to develop secondary crests since temporal dispersion due to the variability in muscle fiber conduction velocity [Eccles & O'Connor (113)] would show increasingly pronounced effects the greater the conduction distance.

The findings of Jarcho and co-workers thus present interesting possibilities for explaining the occasional appearance of so called "polycyclic" potentials of long duration and complex contour during voluntary activation of single motor units in normal man (104, 105). And it is possible that some of the facial muscles normally have their end plates segregated at two "poles" of their motor units, since complex potentials are more commonplace in them than in other muscles (103).

Although this type of innervation may occur, the relative scarcity of complex potentials from normal human muscle must be due to one or more of the following factors: (*a*) such an arrangement is uncommon; (*b*) the muscle fibers of the human motor units are not long enough to cause significant temporal dispersion in responses conducted from the two "poles" of the unit; (*c*) the electrodes, randomly inserted, are not sufficiently discriminating or often enough placed in positions favorable for recording complex potentials. Thus it appears to this reviewer justifiable to consider frequent recordings of polyphasic potentials as a sign of abnormality [Weddell *et al.* (104); Jasper & Ballem (103); Pinelli & Buchthal (108)] and a reduction in the incidence of potentials of long duration and complex shape as evidence of a return toward normal innervation. When regeneration had apparently been completed, three to five years after section and suture, Yahr *et al.* (117) observed that the polyphasic features of early reinnervation were no longer apparent.

The experiments of Jarcho and collaborators (116) present both physiological and histological evidence for the innervation of a single muscle fiber by two motor nerve fibers. Although their data are scanty on this point, double innervation must be considered likely in view of more complete histological studies of others (118), the existence of such multiple neural supply in frogs (119), and the demonstration by Hunt & Kuffler (120) of multiple innervation by a different physiological method. The latter stimulated individual rootlets of the ventral roots and recorded the muscle tensions developed. The sum of the forces produced by exciting the components of the ventral roots was greater than that produced by stimulating all of the fibers simultaneously. These studies would suggest the presence of a peripheral overlap and the supply of parts or the whole of a motor "unit" by more than one motoneuron.

The findings noted in the above paragraph add additional complications to the interpretation of the electromyogram, especially of those potentials evoked by supramaximal nerve stimulation. If a diffuse surface electrode happened to be placed near the middle of the length of a large group of fibers innervated from both ends, the two propagated responses should meet and die out, since the stretches beyond the midpoint are now refractory. Such a cancellation in large number of fibers would result in a trough in the potential wave. Presumably such an artefact would not be encountered in reflexly or voluntarily initiated movement, at least not in the normal. It would seem unlikely that central controlling mechanisms would be organized to defeat themselves in the periphery.

The discussion thus far only serves to emphasize Jarcho's (116) excellent summary:

> If this form [of the electromyogram] is to be understood and its pathological variants explained, much information regarding the spread of electrical excitation in striated muscle is needed. When it is known in what portions of a muscle the action potentials originate, in what direction they are propagated and at what velocities, how they are distorted by the conducting medium through which they flow, and how they are transformed by the manner in which they are elicited and recorded, then a more complete explanation of the electromyogram will at last be possible.

Amplitude of potential and amount of activity.—The development of tension by muscle is one of its outstanding properties and one on which its functional status is largely assessed. It was, therefore, obvious that electrophysiologists should attempt to correlate the force exerted by a given muscle, normal or morbid, with electrical activity obtained from it. Thus, Harvey & Masland (88, 89) described reduction of amplitude of the electromyogram during repetitive nerve stimulation in patients with myasthenia gravis. The typical weakness and abnormal electromyogram are understandable, since the disease is characterized by anomalous neuromyal transmission. There is a progressive block at the junctional region, and fewer and fewer motor units become activated as the nervous volley proceeds. A similar diminution of motor unit activity also occurs in other diseases of varied origin.

In his early outstanding electromyographic studies of human muscle,

Buchthal (121) demonstrated that the total electrical output of paretic muscles of diverse etiology was reduced. By means of concentric needle electrodes he showed that even with maximal voluntary effort "single oscillations" were obtained from severely paretic muscles, whereas "transitional states" were the rule in less significantly damaged muscles. When the nervous supply was not seriously altered, maximal contraction provided the "interference patterns" characteristic of normal muscle. These terms simply describe the degree to which motor units were rendered nonfunctional by disease, "single oscillation" referring to the condition where, during attempted intensive contraction, single unit activity was recorded, contrary to the activation of large numbers of units in the normal muscle. A rough correlation was thus obtained in these experiments between muscle strength and amount of electrical activity [cf. Inman, Ralston *et al.* (122) for a criticism of the loose usage of the term "muscle power" when "tension" or "force" is meant].

Functional impairment of muscle function was correlated with the amplitude of the spike potential of muscle partially denervated by peripheral nerve injury (52, 52a) and poliomyelitis (53). Although the average amplitude of the electromyogram of weakened muscle to percutaneous maximal nerve stimulation agreed quite well with the clinical estimate, considerable variability was noted. Some of the gross discrepancies could be resolved because of the physiological and anatomical consequences of regeneration or the depredations of disease, and perhaps in some measure they resulted also from inadequate electrode placement and sampling. One of the more serious defects, however, was the fact that even normal muscle, with which the electromyographic amplitude of weakened muscle was compared, showed significant fluctuations from subject to subject and in the same subject on separate tests (52).

It would now appear from the recent work of Inman *et al.* (122) that some of the variability noted in the previous work might be avoided if adequate precautions are taken to record during isometric contraction, i.e., without allowing the muscle to shorten. The opportunity for these studies was afforded the California Biomechanics Group by amputees with cineplastic muscle tunnels. Pegs, placed in the tunnels of the muscles freed from their bony insertions (required in the preliminary surgery needed for the fitting of prosthetic devices) were led to recording instruments which measured directly the forces exerted by these isolated muscles during varying degrees of voluntary effort [Ralston *et al.* (123)]. In such subjects excellent correspondence was observed between amplitude of electromyogram and muscle tension, provided the muscle was not allowed to shorten. When the muscles were either stretched or very short, potentials did not correspond with tension. Surprisingly, a maximal effort in the stretched muscle gave smaller action potentials than a similar contraction in muscles working at short lengths (122). This effect, though not completely analyzed as yet, seems due in part to the masking of an electromyogram-enhancing effect of stretch

by a simultaneous potential-depressing effect of desynchronization [Libet *et al.* (124)].

The above suggestion of facilitation due to stretch (even though this is masked in the human muscle) would be in agreement with Loofbourrow's (125) results which showed that an increase in electrical activity of cat muscle occurred when the muscles, excited by cortical stimulation, were subjected to stretch. This effect was attributed to increased reflex proprioceptive drive resulting from stretch, a view amply documented by Gellhorn and collaborators (126 to 131). In addition to the central effects, peripheral studies also indicate an increased amplitude of the electromyogram to result from stretch [Ralston *et al.* (132, 133); Libet *et al.* (134, 135)]. From these experiments it is implied that when a short muscle is excited by a supramaximal stimulation to its nerve supply, not all the muscle fibers respond, but that stretch provides a facilitating influence which causes more muscle fibers to contract. The nature of this facilitation is not yet clear but may be due to changes at the junctional transition between nerve and muscle.

Further evidence which seems to demand facilitation of some kind as a prerequisite for the complete firing of the motor unit is also at hand. Kuffler (136) found that the second of two supramaximal motor nerve stimuli evoked an electrical response of the unstretched muscle of the frog which was greater than the action potential produced by the first stimulus. When the muscle was subjected to stretch, there was no difference between the amplitudes of the first and second electromyograms. This is presumably because of the fact that the stretch had produced enough facilitation to cause all of the muscle fibers to respond to the first stimulus. Wagman's (137) recent observation of a similar phenomenon in human muscle is probably also to be accounted for on the same basis of incomplete activation of all fibers of the motor unit without some prior neuromuscular facilitation. These results would be in keeping with those obtained in human poliomyelitis and myasthenia gravis, where it has been shown that some of the fibers of the motor unit fail to respond to every nerve impulse during the course of fatigue [Hodes (90); Pinelli & Buchthal (108); Buchthal & Høncke (138)]. This defect can be partially reversed by stretch [Ralston *et al.* (132)].

The recent data just elaborated are not in complete harmony with classical concepts of the functional organization of the motor unit. It has been assumed heretofore that all of the fibers comprising the unit are thrown into action by the arrival of one impulse at the neuromyal junction. It would now appear that complete activation will occur only in the presence of facilitation of some kind (e.g., stretch or the residual facilitatory influence of previous nerve stimulation, or other factors as yet unknown).

Within the limitations already noted, the amount of electrical activity or the size of the potential is roughly related to tension production, both in normal and in some abnormal conditions. It is, however, well to keep in mind that individual motor units of greater amplitudes than those of normal units have been recorded from partially denervated muscles (139, 108). In-

deed, Yahr *et al.* (117) have found unit potentials as much as ten times greater than the normal amplitude. The opinion is generally held that these large potentials are due to the response of motor units containing more than the standard number of muscle fibers, reorganized in this fashion in the course of regeneration.

The motor units of a partially denervated muscle were found by Van Harrevald (140) to have enlarged as a result of branching from the remaining nerve fibers. Billig *et al.* (141) attempted to improve the muscular function of poliomyelitis patients by the application of these experimental results by the use of a method known as manual "neurotripsy" (nerve crush). Hodes (142) studied patients treated in this fashion by electromyographic techniques.

Duration of action potential.—In summarizing their clinical studies,which have extended over several years and employed many techniques and types of patients, Buchthal & Pinelli (107) emphasize the important variations of potential duration which occur in different muscles of normal individuals. Temperature and oxygen supply, and particularly advancing age [Petersén & Kugelberg (105)] increase the duration of the recorded potentials. In the brachial biceps of children motor units averaged 3.8 msec. while those from a 70 year old person were 7.2 msec. in duration (107). "Sluggish" potentials which attend the loss of youthful vigor may be explained by the work of Wagman & Lesse (87). They measured conduction velocity of nerve fibers in some 80 normal subjects from 3 to 83 years of age. Conduction velocity increased with age until it reached its maximum at about seven years. It remained constant until about the fourth decade, at which time a gradual reduction of the maximal rate of conduction occurred. Beyond 60 years nerve conduction was markedly slowed. These workers suggest (87) that a selective destruction of the largest nerve fibers occurs in the aged, because of: (*a*) a primary degenerative (metabolic) effect, (*b*) as a result of diminished temperature and oxygen supply, or (*c*) as a combination of these factors. The sensitivity of large fibers to the effects of anoxia is well known from studies on isolated mammalian nerves as well as from studies in man [Wagman & Flick (144); Magladery (145, 146)].

Selective destruction of large motoneurons in poliomyelitis had been postulated previously by Hodes and co-workers. Both conduction velocity measurements (slowed) in man (53, 147) and studies of motoneuron size in normal (148) and infected monkey cords (147, 149) support this suggestion in this disease. A similar effect of various other noxious agents may recommend the idea of neuronal destruction on the basis of size as a biological phenomenon of some general importance [cf. Hodes (53, 149) for further discussion of this point].

In certain neural or muscular derangements there is a tendency to the production of action potentials of shorter than normal duration. Spontaneous fibrillation potentials which occur in denervated muscle, as described by Denny-Brown & Pennybacker (85), Weddell *et al.* (104) and others, are no-

torious examples of short-lasting (as little as 0.5 msec.) spikes. Since the fibrillation potential represents the ultimate in the fractionation of the muscular response of the total motor unit, its brevity is easily understood.

Other pathological states in which there is reduction of the number of functional elements contributing to the motor unit potential, will also yield abbreviated responses. From patients with muscular dystrophies, in which there is diffuse and irregular destruction of muscle tissue, unit potentials are shorter than normal. Kugelberg (110) considers this finding pathognomonic of the disease. Buchthal & Pinelli (107) agree in part with this interpretation, but they tentatively suggest a possible differentiation of muscular dystrophy into two groups on the basis of whether the unit potentials persist for the normal period or are abbreviated. Although studies of several types of inflammatory processes in muscle fit in with the idea that the more fleeting unit potentials are a direct result of the reduction of the number of contributing fibers, certain discrepancies have been noted which require considerably more investigation (107).

Of considerable importance in the pathophysiology of neuromuscular function is Buchthal's discovery of potentials of greater than normal duration in diseases which primarily involve the spinal cord (121, 138, 150). He distinguishes these central defects from neural disorders of the periphery (neuritides and traumatic injury) in which the potentials are usually within the normal range of duration. They are also distinguished from junctional or muscular maladies in which the time course of the unit potential is either normal or reduced (p. 154). Buchthal's group recorded from several places in the muscle simultaneously, and believe that some motor units are "synchronized," i.e., discharge together, in cord diseases. Derangement of central control is thought to be brought on by the insults to which the cord was subjected as a result of the pathological agent.

Denny-Brown (71) and Kugelberg & Taverner (151) do not consider the work of Buchthal and his collaborators conclusive on this point. The former believes that the synchronization could be an artefact. For it is possible to record the same unit more than once when the muscle is atrophic. He also objects on the ground that one can not observe, palpate, or record tension of synchronous twitches from discrete motor units in conditions where the electrical synchrony is noted. (Considering the size of the unit as compared with the total muscle mass, it would not appear that inability to record discrete tension changes is a serious objection.) Since Kugelberg & Taverner (151) applied slowly rising currents to peripheral nerves of subjects with neural disease of both spinal and peripheral origin and observed synchrony of motor units in both types of disease, they do not agree that this response arises from disordered central organization. Rather they suggest that the defect may be junctional or muscular.

It appears to this reviewer that Buchthal & Madsen's re-investigation of the problem has largely met the objections of both critics (152). Muscles rendered atrophic by peripheral nerve damage showed synchrony in only

about 20 per cent of a large number of placements (being similar to the synchronization found in normal muscle) whereas over 60 per cent of the potentials were beating in unison when they were recorded from patients with cord disease. This was true in spite of the fact that in many cases the degree of atrophy was greater in afflictions of peripheral origin than in those produced by a central defect. It is thus difficult to entertain Denny-Brown's (71) suggestion on artefacts in atrophic muscles. The mere production of synchrony by peripheral stimulation does not in the least argue against the central origin of the condition, as Kugelberg & Taverner (151) appear to indicate. It is quite possible that hyperexcitable nerve fibers are also present in cord diseases which render muscles atrophic. Such peripheral hyperexcitability may even be considered a secondary reflection of the diseased state of the centers. Nor does Kugelberg & Taverner's (151) statement that these nerves are not hyperexcitable appear to be valid. Since the largest nerve fibers are destroyed in two of the conditions they studied, poliomyelitis (53, 147, 149) and amyotrophic lateral sclerosis (153), the threshold of the intact smaller fibers could not be properly assessed by their methods.

Thus, although the finding of synchronization appears somewhat more difficult of interpretation than Buchthal's group originally proposed, there appears little doubt that the frequent occurrence of this phenomenon is grounds for suspecting the presence of central nervous system disease. Pinelli & Buchthal (108) have indeed already attempted to use this observation for estimating the degree of central damage as well as for prognosis. They found that those muscles of poliomyelitis patients which showed significant improvement one year after the onset of the disease were those in which potentials of normal duration (i.e., little synchronization) predominated during the first month of the disease. Those muscles from which increased synchronization was obtained early in the disease did not go on to significant recovery at the end of one year.

Further work is needed to explain the occurrence of synchronization in about 20 per cent of normal large muscles, the extremely high incidence of the phenomenon in small muscles of the hand, and its presence in some cases of peripheral nervous disease.

The coincident beating of more than one motor unit may well be one of the important causes of potentials of long duration (which are also often of greater than normal amplitude). However, in order not to make for that spurious simplicity which is the last refuge of the complex, the various other factors which have been noted (selective destruction of large neurons or fibers, temporal dispersion, decreased temperature, oxygen lack, abnormal reorganization into large motor units, etc.) should be borne in mind constantly.

"*Lagniappes.*"—The merchants of olden times (pre-inflation, i.e.) would on occasion present a dividend to their faithful and bounteous customers, such as a thirteenth egg for the price of a dozen or a free candy bar for the customer's progeny. Although this delightful custom has regrettably van-

ished in the age of super-markets, the former practice is still memorialized by the use of the term "lagniappe" in the current speech of Louisiana. In a very real sense numerous lagniappes have been presented to physiology by the active investigators in electromyography. It still remains perhaps for the sensitive and observant physiologist to recognize these dividends for what they are and to convert their present promise into future solid physiological advances.

Several examples of outgrowths of human electromyography (conduction velocity, neuromuscular junction, stretch studies) already have been noted casually in the preceding pages. In some instances, human studies have verified animal experimentation. In others, data from animal work have been extended or clarified, while in still other cases novel facts and theories have been brought to light by means of these researches on intact human subjects or conscious patients. In the following discussion, a few excerpts of material which seem especially pertinent have been culled to suggest potentialities available with electromyographic technique. Doubtless many additional noteworthy contributions should have been included in this section, but the examples chosen reflect personal preferences and also represent selection from the literature which the writer came upon to a certain degree by chance.

The preliminary studies of Wagman dealing with nerve conduction and electrophysiological reflex examination during normal human growth point the way towards interesting future developments in the much-neglected but increasingly important field of geriatrics. The demonstration (87, 154) that peripheral conduction time, after about seven years of age, depends upon the length of the body would seem obvious enough. But it should be mentioned that the contrary opinion of constant conduction time during growth had been previously maintained (10). From theoretical considerations of nerve function (based on the importance of internodal length in conduction) Rushton (155) suggested that reflex time might remain constant during the development of the normal individual. This supposition was also shown by Wagman to be in error (102).[1] It is to be hoped that future studies will consider afferent innervation as well as the motor supply and that they will be extended to include investigation of junctional properties and motor unit organization during growth. It is clear that a better understanding of the peripheral determinants of behavior during maturation and senescence will be facilitated by such research.

The difficult problem of recording the spike potentials from human nerves has been solved simply and ingeniously by Dawson (158, 159, 160). High amplification is necessary to record the small potentials available from nerves (especially with the requirement that they be picked up through the

[1] Parenthetically, it should be added that Rushton's (155) theories of nerve function are refuted also on other grounds, as, e.g. on the relationship between diameter and spike amplitude [Gasser & Grundfest (33)] and diameter and conduction velocity [Gasser & Grundfest (33); Gasser (156); Hodes (157)].

large shunt of the skin over the nerve). With such high gain it was impossible to decide whether a particular hump on the oscilloscope trace was a true response to the nerve stimulation or whether it was due to the inherent random noise and instability of the amplifiers. Dawson & Scott (158, 159) therefore employed the clever expedient of repeating the stimulus regularly and photographing 50 to 100 individual sweeps on a single picture. Instrumental artefacts were thus statistically balanced out by this superposition method, while the nerve response stood out clearly as a peak with reasonably constant latency, amplitude, and form. Dawson (161) had previously evoked action potentials from the human cortex by stimulation of various peripheral nerves. The recordings were made from the scalp by the superposition method already described. Conduction rates in the fastest fibers of the peripheral trunks were easily determined by stimulating the nerves percutaneously in two accessible regions and noting the latency difference between the cortical responses to proximal and distal excitation.

In the opinion of this reviewer, Magladery's researches represent a high point in analytic human neurophysiology. His work, performed almost exclusively on normal subjects, has been presented in seven original papers (16, 17, 29, 79, 100, 145, 146) and one partial summary (162). Because of the wealth of material it is somewhat difficult to decide which contributions from Magladery's group should be stressed in this report. The following items are some which stand out in the writer's memory.

Magladery, McDougal & Stoll (145, 146) studied the effects of ischemia and made observations in the postischemic state. Differential susceptibility of motor and sensory nerve fibers to anoxia, as well as the greater resistance of distal nerve segments (smaller fibers) than of proximal regions to circulatory arrest were shown. The familiar ischemic paresthesias were investigated and thought to result from hyperirritability of end organs, perhaps as a result of potassium shifts during and following the ischemic period. Motor aspects of the post-ischemic state (repetitive discharges) were also studied by this group [see Kugelberg & Cobb (163) for a similar study with somewhat different conclusions].

Magladery & McDougal (79) described "H reflexes"[2] which seem to be identified with the well known stretch reflex. However, the fibers of the afferent limb of the arc conduct at 60 to 70 m./sec. instead of at approximately 120 m./sec., as determined by Lloyd (164, 165) in experimental animals. The distal tapering noted is interesting and Magladery & McDougal (79) point out that even more attention must be given to this fact when studying human nerves since they are so much longer than those of the customary labo-

[2] The H wave is observed in human calf muscles following submaximal stimulation of the posterior tibial nerve in the region of the popliteal fossa. This muscle potential occurs about 20 msec. later than that which results from direct stimulation of the motor fibers of the posterior tibial nerve. Its amplitude is reduced as the stimulus intensity is increased. The H wave is the motor expression of the H reflex which is identified with tendon reflexes and is probably monosynaptic.

ratory animals. It seems unlikely, however, that the nerve could taper sufficiently from cord to popliteal space to account for a discrepancy in conduction rates of 60 to 70 m./sec. (man) to 120 m./sec. (cat).

Insulated needles were inserted intrathecally at several spinal levels in normal volunteers (100). By means of this heroic procedure, Magladery's group could record dorsal root, cord, and anterior root potentials following peripheral nerve stimulation. Because of the technical difficulties, Dawson's (161) superposition technique was employed. With these methods it was possible to prove that the inhibitory effect of stretch[3] or afferent stimulation (16) on the two-neuron arc was not caused by depression of notoneuron excitability by antidromic impulses [Renshaw (166)]. For no evidence of antidromic activity was recordable from the intrathecal electrodes when the reflex was inhibited.

When the afferents of the tibial nerves were excited both facilitation and inhibition of the two-neuron arc were noted. Inhibition of the monosynaptic reflex occurred if the high threshold (group II) afferents of the plantar nerves were excited (16, 17). Of considerable interest is the fact that increasing the strength of stimulus applied to the plantar nerves facilitated the two-neuron arc. This is probably accomplished by complex multisynaptic pathways. The effect thus appears to have a different mechanism from the facilitatory influence of group I afferents which act directly on the motoneurons.

Park, Teasdall & Magladery (29) found that brief stretch produced an initial facilitation of motoneuron excitability which was followed by a profound depression. These workers believe that some of the effects of stretch must, therefore, be carried in group II afferents and traverse polysynaptic paths.

The afferents in the plantar nerves supplying the small foot musculature do not seem capable of evolving the two-neuron arc (H reflex[2]) but rather yield the "F reflex"[4] which is also thought to be myotatic (79). The afferent fibers serving these reflex arcs conduct even more slowly than do those of the monosynaptic H reflex[2]. The former reflexes have been observed in patients in whom the usual tendon reflexes employed clinically, as well as the H reflexes,[2] are absent. The fact that these patients ambulate well, perform fairly dexterous movements and present no striking postural deficits has led Magladery & McDougal (79) to suggest that they may represent an important reflex contribution to the control of posture and movement. If true, this would tend to de-emphasize the assumed overwhelming significance of the two-neuron stretch reflex in man (167).

[3] Painful stimuli did not inhibit the two-neuron arc.

[4] The F waves are reflex in origin and are recordable from the hypothenar muscles when the ulnar nerve is stimulated, from small foot muscles when the posterior tibial nerve is excited, and from anterolateral muscles following a peroneal nerve volley. Unlike the H waves, the F waves increase in size as the stimulus strength is increased. The afferent limb of the F reflex is subserved by smaller fibers than those of its motor limb. This is in contrast to the H reflex, where the reverse is true.

The brief summary just presented is meant merely to indicate the scope of Magladery and co-workers' interests and to suggest strongly that there is no substitute for examining these papers carefully and in their entirety.

Conclusion

This review has covered some of those studies which have brought closer to realization the prospect of adequate physiological examination of the human nervous system. A good approximation to quantitative study is now possible by researches on the muscle, neuromuscular junction, afferent, and efferent conduction and excitability, the state of reflex centers in the cord, and arrival of information from the periphery at the sensory cortex. There is a current tendency for clinical observers—neurosurgeon, neurologist, and psychiatrist—to apply the fruits of neurophysiological research ever more boldly to their problems. With increasing collaboration, based on mutual respect and sharing of privileges, responsibilities, and facilities, between laboratory and clinic, it is perhaps not too much to hope that ever more complex functions of the nervous system will come under concerted attack, to the benefit of all.

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BLOOD VOLUME MAINTENANCE AND REGULATION[1,2]

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For many years clinicians have regarded the chemistry of the blood almost entirely in terms of concentration. Their colleagues in the clinical laboratory produced data on grams of hemoglobin, milligrams of dextrose, volumes of carbon dioxide, etc., but again, customarily expressed as the quantity per one hundred milliliters of blood or plasma.

With the advent of methods for estimating body fluid volumes, however, it became feasible to consider body chemistry in terms of actual quantities, such as total grams of circulating protein, or total grams of available hemoglobin. As improvement of pre-existing methods and development of new techniques have enabled the laboratory staff to report reliable, reproducible data, the clinician has placed increasing reliance upon their use (1). The concept of total available quantities of body constituents has significantly altered the clinician's approach to the vital problems involved in assessing body fluid imbalance and the requisite replacement therapy. He has observed that physiologic mechanisms apparently operate in maintaining as nearly as possible normal concentrations and osmotic relationships, especially within the cells, and that the total volume of body fluid is frequently altered to achieve this balance (Beling *et al.* (2)). Consequently, while the existence of fluid imbalance is deducible from history and physical signs, only measurement of volume and solute concentration together will yield reliable estimation of its magnitude.

Methods for the Measurement of Blood Volume, Plasma Volume, and Red Cell Volume

The earliest studies in animals were done by exsanguination by Valentin (3). The earliest human studies were done by Haller (4) in 1854, who exsanguinated two criminals. The majority of the methods employed for blood volume measurement stem from the dilution principle, wherein a measured, small quantity of easily identified, nontoxic material is introduced into the bloodstream and the degree of dilution determined. Three types of analysis are possible; direct measurement of plasma volume, and calculation of blood volume using the hematocrit; direct measurement of the red cell mass

[1] The survey of the literature pertaining to this review was concluded in July, 1952.

[2] The following abbreviations are used in this review: PVP (Polyvinylpyrrolidone); Tm_{PAH} (tubular maximum for *p*-aminohippurate).

with calculation of blood volume from the hematocrit; and finally, both plasma and red cell volume may be determined directly and simultaneously. Suitable materials for the above measurements are of two classes: (*a*) those substances with a strong affinity for combining with plasma proteins or with a similar molecular weight range and, therefore, assumed to have a comparable distribution volume; (*b*) secondly, means of marking red blood cells, either naturally occurring erythrocytes with special characteristics that are distinguishable, or substances that can be incorporated as a tag in the preformed red cell.

Materials used for plasma volume tagging include acacia, PVP[2], antitoxin, introduced by von Behring (5), and dye substances. The initial measurements using brilliant vital red were reported by Keith, Rowntree & Geraghty (6). Dawson, Evans & Whipple (7) suggested using the blue dye T1824. Fine & Seligman (8) reported the initial observations using radioactive iodinated serum albumin.

Determination of red cell mass by the use of carbon monoxide was reported in 1882 by Grehant & Quinquand (9). Ashby (10) determined blood volume using differential red cell typing. Hahn & Hevesy (11) reported determination of red cell volume utilizing radioactive phosphorus as inorganic phosphate, and in 1941 Hahn and his associates (12) employed radioactive isotopic iron to tag red cells during erythropoiesis, and subsequently utilized the marked erythrocytes of the donor for red cell mass estimation in other subjects. Jope (13) suggested using erythrocytes exposed to hydrogen sulfide, since sulfhemoglobin formation caused differential staining of the erythrocytes upon routine staining of blood smears. Sterling & Gray (14) recently advocated use of the radioactive isotope chromium-51 as an erythrocyte marker. The mere multiplicity of suggested methods coupled with subsequent controversy has sown seeds of doubt in the minds of many regarding accuracy and utility of any blood volume technique. The voluminous literature may also be entered as evidence for the recognized importance of volume measurements and, as Reeve (15) and Gregersen (16) have both indicated in their careful analyses of this field, it is fortunate that the majority of the methods mentioned do give values sufficiently accurate for clinical use.

All procedures designed to measure blood volume have several sources of potential error in common. Since correct estimation of the degree of dilution is predicated upon uniform mixing of the test substance throughout the fluid volume in effective circulation at the time of observation, failure to deliver the calculated amount of test material into this circulation will invalidate the data. Certain abnormalities, such as arteriovenous fistulae, in the vascular tree may prevent adequate mixing within the customary lapse of time. Theoretically, the "ideal substance" for fluid volume computation should be metabolically inert, in addition to being firmly and selectively bound by some naturally occurring substance whose apparent volume of distribution corresponds to that undergoing study. As yet, the perfect

material has not been found, and in all techniques, one observes progressive disappearance of the tagged element by various routes, including metabolic participation, movement across the limiting membrane bounding the fluid space, by phagocytosis and by excretion. Fortunately, the rate of loss is usually low and is constant within practical limits for the test material used in the individual subject during the observation period. This permits one to extrapolate back to "zero time" on a graphed concentration/time curve. [The theoretical concentration value so derived is the value anticipated in the absence of any loss and assumes instantaneous and complete mixing.]

From studies of red cell volume measured with carbon monoxide in dogs with calculation of red cell volume coincidentally from hematocrit readings and plasma volume determined with brilliant vital red, Smith, Arnold & Whipple (17) concluded that hematocrit readings observed in peripheral venous blood samples overestimated the cell/plasma ratio. This explained the comparatively smaller red cell volume obtained by direct measurement. Although subsequent reports (18) indicate that carbon monoxide and T1824 plasma volume-hematocrit estimations of red cell mass are probably not significantly different when averages of a number of observations are compared, the red cell distribution data obtained by Gibson and his group indicate marked differences in hematocrit readings of blood samples withdrawn from various organs (19).

Simultaneous direct determinations of red cell and plasma volumes by a number of investigators have furnished confirmatory evidence. Higher cell (cell/cell plus plasma) ratios were found in blood samples taken from peripheral veins, as compared with this ratio for the circulating blood (20). Nickerson *et al.* (21) recently made simultaneous volume measurements in the dog using T1824, carbon monoxide, and radioactive Fe^{55}, obtaining carbon monoxide volumes 2 per cent above the T1824 volumes, while Fe^{55} volumes fell 11 per cent below T1824 values. Excellent technique in their hands gave checks within one-half of one per cent for *in vitro* Fe^{55} estimation of a theoretical 50 ml. volume. Since evidence as to routes of removal of these various materials from the blood or their possible metabolic removal is most fragmentary, and since varying figures for the "total body hematocrit" have been observed, it seems advisable to refer to such data in terms of ratios of cell volume to cell volume plus plasma volume in calculating the effective circulating blood volume under any given set of experimental conditions. Hahn, Bale & Balfour (22) reported a linear relationship between venous hematocrit readings and Fe^{55} red cell mass values for the physiologic range.

In assessing animal data on red cell volumes, the advisability of splenectomy before undertaking any experimental procedures must be recalled. Hargis & Mann (23) reported the significant contractions observed in a plethysmographic study of the dog spleen with a concomitant shift in the circulating red cell mass. Huber (24) confirmed this with observations upon

dogs subjected to graded hemorrhage. Estimation of red cell mass may be further complicated by factors resulting in trapping of unknown portions of the erythrocyte volume, as observed by Gibson and his group, when capillary blood flow decreased during experimental shock in the dog (25).

Recent reports have stated that significant differences exist in the degree and occurrence of decreased blood flow relative to the observed pseudo-agglutination or "sludging" of red cells in the circulation. Hemorrhagic shock is characterized by a marked decrease in blood flow progressing with severe shock, while intravascular clumping of red cells does not appear until effective capillary blood flow has ceased. Thermal burn shock results in early appearance of such red cell masses while blood flow is sufficiently active to carry such masses into tissue capillaries [Bigelow, Heinbecker & Harrison (26), Brooks *et al.* (27)].

Interference with erythrocyte mass measurements is reported by Nickerson and associates (28) when an unsuspected incompatibility is found upon injection of Fe^{55}-tagged red cells into a recipient, with consequent agglutination of a portion of the tagged red cell mass. The observed red cell mass values were abnormally low, even in the absence of objective or subjective evidence of reaction, other than agglutination. These workers detected similar aberrations when incompatible cells tagged with carbon monoxide were used, but found no interference with T1824 values. Michie and co-workers (29) found that during a fairly marked pyrogenic reaction, which followed passage of a catheter for renal clearance studies, a markedly aberrant dye concentration/time curve was obtained.

In view of these technical problems associated with red cell agglutination, similar difficulties may occur when red cell volume estimation is attempted shortly after the subject has received an infusion of certain plasma volume expanders. Preparations of certain lots of these materials contain disproportionately large amounts of higher molecular weight aggregates (in the range of 100,000 to 250,000), responsible for the pseudo-fibrinogen properties of these substances. Recent reports of plasma volume increments following infusion of 6 per cent dextran, in certain instances, include data listing disproportionately large plasma volume increases, two to five times greater than the volume of the dextran solution infused (30). Nevertheless, one must acknowledge the value of comparative studies for measuring relative change when the same technique is used under properly controlled conditions.

In evaluating the blood volume deficiency encountered in the majority of seriously ill patients, one must set a value for the magnitude of the "theoretical average normal blood volume" which would obtain for an individual of similar habitus in good health. Critical errors may occur, especially in those individuals with bodily proportions at either extreme of the height-weight range, or in the chronic invalid. Since effective circulating blood volume is correlated closely with the mass of metabolically

active tissue, an approximation sufficiently accurate for average clinical use may be derived by measurement of the patient's height, and by then calculating a theoretical normal blood volume for an individual of average normal weight for the patient's height. Gibson & Evans in 1937 confirmed such correlation in a detailed study of 90 normal subjects (31). Behnke (32) subsequently determined the specific gravity of men with a variety of bodily conformations, obtaining useful data on the relative proportion of fat and lean body mass. Perera in 1946 (33) reported the effect of significant weight change on predicted plasma volume. A significant volume increase was noted only with an increase in lean body mass. Hardy & Drabkin (34) also reported the anticipated correlation of lean body mass with interstitial and intracellular fluid volumes in man, and their T1824 plasma volume figures and blood volumes by hematocrit calculation illustrate quite clearly the variability in observed volume/weight ratios (ranging from 70 ml. of blood per kg. of observed weight in very obese subjects, to 105 ml. of blood per kg. of actual weight in extremely thin persons). Brozek & Keys have recently published their studies of physiologic changes occurring in body composition with advancing age (35). Body specific gravity figures, obtained upon a group of men in middle age having weights within 10 per cent of the average normal for their age, were observed to decline progressively with aging. A value of 1.082 was determined for the age range of 18 to 22 years, whereas the figure was 1.044 for a comparable group of subjects with an age range of from 53 to 57 years. These data correspond quite convincingly with Sarkisian's data for submarine personnel, an average body specific gravity of 1.063 for personnel between 18 and 22 years of age, whereas, this figure had descended to 1.044 in the subjects between the ages of 33 and 37 years of age (36). Data upon parallel reductions in residual air volume have been observed, and additional data upon the above age-specific gravity relation are being accumulated which will account for this residual air decrement as well as for other factors.

With reference to effects of significant change in actual body weight upon body composition and upon some fundamental values for the circulating blood, Taylor *et al.* (37) have just presented their findings on force feeding and composition of weight gain in a group of physically healthy subjects with schizophrenia. Four of the seven subjects added an average 18.2 kg. (40 lb.) to their control weight over a six months period during which maximal caloric intake was maintained. At the end of this period, body specific gravity figures indicated a 13.3 kg. increment in fat and a 4.9 kg. increase in lean tissue. Blood volume increased by somewhat over 500 ml. while cardiac output rose from 4.36 to 4.87 l. per min. in these obese subjects.

Chronological age of the patient bears less significant correlation with blood volume than does biological age or physical fitness. Taylor *et al.* (38) reported a 10 per cent decrease in the blood volume of healthy young male subjects placed at absolute bed rest for two weeks. While 85 to 90

ml. of blood per kg. would constitute a normal blood volume for the man engaged in active physical labor, the sedentary person will have 80 ml. per kg. or less (39).

Plasma volume was determined principally with dye dilution methods, until the availability of radioactive isotopes permitted the use of tagging materials, such as I^{131} incorporated into human serum albumin, first reported from Fine's laboratory (8). Hooper and co-workers (40) in 1920 had investigated the behavior of dyestuffs in plasma, chiefly brilliant vital red during their early studies. Dawson, Evans & Whipple (7) examined a large series of dyes and concluded that diazo dyes possessed the requisite properties. They suggested specifically employment of the blue dye obtained from the reaction between ortho-toluidine (dimethylbenzidine) and 1,8-aminonaphthol-2,4-sulfonic acid (hence its designation as "T1824"). Gregersen, Gibson & Stead (41) and many others investigated its use in detail, confirming the reproducibility of data obtained, and also calling attention to some characteristics of its disposition after injection into the blood stream. A highly irregular initial dye concentration/time curve appears immediately, and then smooths out into a logarithmic curve within the first one to five minutes. This initial irregularity, ascribed to mixing phenomena, has been interpreted by Cruickshank & Whitfield (42) as evidence of phagocytosis of a significant, unknown portion of the injected dye dose, and as responsible for discrepancies between dye blood volume values and those obtained using other tagged material. Cruickshank and Whitfield advocated blockade of the reticuloendothelial system prior to dye volume analyses and reported plasma volume and blood volume figures approximately 10 per cent lower following india ink blockade in cats, or repeated T1824 injection in human subjects. Reeve & Armin (43) were unable to substantiate any consistent blockade effect. Miller in 1947 (44) also could not demonstrate a significant difference in T1824 volumes obtained serially on the same subject. Furthermore, his measurements of dye concentration in liver bile indicate that less than one per cent of the T1824 injected is excreted by this route within the first two to five hours following administration. Furthermore, the regular, stepwise increment in dye bile concentration during serial volume determination is evidence that the liver phagocytes are not saturated by the dye dosage customarily employed, even when repeated several times within a short interval of time.

After the initial mixing period T1824 dye concentration/time curves show a smooth slope, usually with a decrease of about 3 to 11 per cent per hr. ascribed to the passage of T1824, bound to albumin, through capillary membranes into the lymph. Rawson (45) published data indicating that T1824 is bound rapidly and firmly upon introduction into the blood stream. LeVeen & Fishman (46) subsequently observed binding of the dye by globulin *in vitro*, and stated that the bond appeared to be easily dissociable, thereby theoretically making the material unsuitable as a metabolic tracer. The consensus at present, however, is that the dye-protein bond is sufficiently

firm to preclude the existence of any significant amount of free dye within the circulation. Ultimate disposition of T1824 by the body has not been determined. Werner & Horvath (47) recently reported studies of the dye disappearance curve in normal and hepatectomized dogs, and observed no significant alteration.

Some investigators have questioned the reliability of T1824 plasma volumes determined at such short intervals that each new dye-concentration/time curve rises from the baseline of pre-existing dye concentration. Smith in 1920 (48) reported no interference with the repeated estimation using brilliant vital red. Subsequent publications by several different workers have established the feasibility of serial determinations with T1824 dye (42, 44, 49). Allen & Gregersen (50) reported observations on dog plasma volumes. By using very high dye concentrations they found the volume distribution independent of dye concentration up to and above levels of 1 mg. of dye per ml. of plasma. While they found that dye levels of 1.6 mg. per ml. and over resulted in hemolysis of 50 per cent or more of the dog's erythrocytes, human red blood cells were unaffected by as much as 4 mg. of dye per ml. of plasma or saline. The usual routine test dose of 10 mg. of T1824 produces a level of 0.06 mg. of dye per ml.

The dye diffusion slope of 3 to 13 per cent per hr. is usually reproducible for an individual patient from day to day, and the degree of slope is not correlated with shock or altered capillary permeability [Noble & Gregersen (51)]. Examination of a large body of data, accruing from routine preoperative volume estimation on an active surgical service, indicates that approximately 5 per cent of patients with apparently adequate and stable circulation will have dye losses as great as 25 to 30 per cent per hr. for no known reason (39). Similarly, an equal number will have essentially no measureable dye loss within a 2 hr. observation period. Gregersen (52) believes that for this type of study a single dyed plasma sample, drawn at 10 min. following injection, will yield volume estimations with sufficient accuracy for clinical estimates of blood replacement needs. Gregersen and others (53) studied the optical properties of the dye solutions in normal plasma with concentrations of chloride and protein encountered in the physiologic range, and concluded that standardization of the dye in a plasma sample of the individual subject was unnecessary. As Gregersen carefully emphasized, their data were obtained from normal subjects and this conclusion applies therefore to normals.

The occurrence of variable traces of chromogens other than T1824 in the commercial lots of this dye require that the investigator standardize each dye lot in a sample of pooled normal plasma as described by Leeson & Reeve (54). Some investigators have found that, in patients entering hospitals for general surgical procedures, the determination of the wave length of maximum light absorption and measurement of optical density of a known volume of the individual patient's plasma, into which a known amount of T1824 has been placed, gave more accurate results.

Walker (39) reported that individual determination of possible plasma effect upon optical properties of the dye had been found necessary in carrying out preoperative plasma and blood volume determinations on a sizeable series of general surgical patients seen in the past five years. In 61 per cent of patients studied, the individual's plasma had no significant effect upon the dye, while in 16 per cent an error of over 7 per cent in volume estimation would have resulted if an individual dye-plasma standardization had not been set up. In the remaining 23 per cent of cases, an average error of 4 per cent in volume measurement would have been incurred by failure to determine the effects of the individual's plasma. However, the standard error for plasma volume estimation was plus or minus 2.8 per cent. Unfortunately, we have no means of identifying those individuals whose plasma will have an effect from the 65 per cent in whom it has none. The two additional technical points of significance are the advisability of drawing a minimum of three dye-plasma samples permitting analysis of the dye concentration/time curve, and delivery of the 10 mg. dose of T1824 from a syringe and needle weighed before and after dye injection.

The reading of correct optical densities for dyed plasma samples may be altered by hemolysis or by the presence of lipaemia. Morris (55) reported that the T1824 content of plasma samples, containing sufficient free hemoglobin to interfere with spectrophotometry, could be determined by chromatographic separation of the dye. Nicholson & Nahas (56) have recently reported cardiac output and blood volume studies where T1824 plasma concentration was determined in a special cuvette designed for the Beckman spectrophotometer, in which an aliquot of the whole blood sample was laked with saponin and optical density measured at 540 mμ for hemoglobin computation, as well as at 625 mμ for dye concentration calculation. With this technique, correcting for hemoglobin interference in the estimation of optical density for the dye, they obtained a three per cent co-efficient of variation for measurement of the change in plasma volume in 30 subjects. This degree of accuracy was obtained throughout a dye concentration range of 3 to 25 mg. of T1824 per l. of plasma.

T1824 extraction techniques have been applied both to dye concentration estimation in the presence of hemolysis and of lipemic turbidity (57). Until recently none of the methods suggested have produced ideal data because of inability to extract the dye quantitatively. Allen (58) introduced the use of paper pulp absorption, which is reported as approximately 97 per cent efficient in removing the dye; in addition, this removes all interfering substances so that dye concentration is then determined from the clear solution in which T1824 is eluted from the paper.

Krieger *et al.* (59) compared the plasma and blood volume values, and the rates of fall of blood concentration of T1824 and of I^{131}-tagged albumin. In their data, T1824 blood volumes are approximately 5 per cent higher than blood volumes simultaneously determined with I^{131}-albumin. This volume difference is attributed to the initial rapid loss of T1824 from the

bloodstream, either by phagocytosis or rapid diffusion of the free dye within 1 to 5 min. following injection before albumin binding is complete. Their studies, however, included only a single sample technique at 10 min. in T1824 volume estimation. Analysis of their data shows that disappearance rates of the iodinated albumin and of T1824 are equal and parallel. Both disappearance curves start at 4 to 6 per cent loss per hr. during the first 5 to 10 min., and then become logarithmic functions as loss proceeds. Mayerson & Wasserman (60) re-examined the disappearance rate of I^{131}-albumin and concluded that a three component, exponential expression fitted the data. Approximately 20 per cent of tagged albumin had left the blood at five hr. after injection. Repeated injections of I^{131}-albumin produced disappearance curves similar to that following the initial injection (61). The radioactivity was first detected in thoracic duct lymph about 10 to 20 min. after injection, dependent upon rate of lymph flow. For a period of some 40 min., I^{131}-albumin concentration in such lymph increased rapidly. This has tentatively been ascribed to mixture of lymph entering the thoracic duct from hepatic drainage. In a second interval of approximately 70 min., concentration increased at a slower rate, indicating mixture of intestinal lymph drainage. A third period, terminating at about 14 hr. after I^{131} injection, was characterized by only a slight increment of I^{131}-albumin, presumably representing establishment of equilibrium. After 14 hr., radioactivity decreased proportionately in lymph and in plasma.

Factors Influencing or Regulating Blood Volume

The basic concept of an "effective circulating blood volume" appears useful, for the potential capacity of the vascular reservoir far exceeds the fluid volume available for filling it under ordinary circumstances [Landis & Hortenstine (62)]. Diminished venous flow and increased venous pressure lead to increased filtration rates in capillaries, as well as pooling of blood in venous channels. Positive pressure breathing diminished blood volume 12 to 14 per cent (63). Of this fluid loss, approximately one-half is lost across the capillary barrier. The calculated fluid loss is sufficient to raise hematocrit readings 4 to 10 percentage points above initial readings. By approximation a 2 to 5 per cent reduction in blood volume may be considered to occur with each 10 cm. venous pressure rise, if maintained for a 20 min. period.

Drew, Dripps & Comroe (64) demonstrated the value of blood volume studies in reporting the effects of morphine as employed clinically in exaggerating the response to tilting, to the erect posture, or to pressure breathing (65). We know little of the means by which these external stimuli are appreciated and quantitated by the organism. However, a number of chemical or mechanical stimuli have been proven to influence the effective circulation, even though we have not as yet finally identified the end organs in each case. The pressure receptors in the carotid body, the aortic arch receptors responding to chemical changes in the blood, related to oxygen and carbon dioxide content, are examples of some of the ways in which environmental

stimuli may be operating. Carlson *et al.* (66) have reported the apparent adaptation of human subjects to intense cold when exposed over long periods of time by changing the amount of blood passing through peripheral superficial areas, as compared to that circulating through muscles.

The demonstration of blood volume changes during anesthesia is correlated also with renal function, which permits an explanation of the changes noted in urine volume with reference to posture or pressure breathing. Henry & Gauer (67) suggested on the basis of studies during pressure breathing that there might be intravascular receptors located in the low pressure side of the cardiovascular system. Sieker, Gauer & Henry (68) have also studied the opposite set of circumstances in their investigation of renal function during negative pressure breathing in man. While breathing at a pressure of -15 cm. H_2O for 45 min., human subjects showed marked diuresis, urine volume increasing over three times that of the control period, while total sodium excretion increased only 15 per cent. They attribute the increased urine flow to a renal response, mediated in a manner as yet unknown, following engorgement of the hypothetical receptors in the thorax. Guyton (69) has recently published data on rhythmic fluctuations in vasomotor activity. Previous studies had shown that arterial blood pressure oscillations were being recorded on dogs under circumstances which could explain such findings through the stimulation of a presso-receptor-autonomic reflex. His present report is based upon observation of 19 dogs in whom cerebrospinal fluid pressure was raised to 120 mm. Hg, a level well above arterial blood pressure. When the central nervous system was made ischemic, vasomotor waves over 100 mm. Hg. were recorded, their duration being over 20 sec. (70).

The bodily responses to changes in posture seem to indicate existence of a receptor, sensitive to intravascular volume changes. Goodyer, Peterson & Relman (71) noted a decreased rate of sodium excretion, as well as occasionally a decrease in rate of water excretion, when a normal subject received an infusion of a hyperoncotic solution of purified human serum albumin. In explanation, they postulated an increase in plasma volume, at the expense of a decrease in extracellular fluid, sufficient to increase interstitial fluid tonicity thereby stimulating an osmoreceptor. Welt & Orloff (72) confirmed these findings, concluding that a pressure receptor as well as an osmoreceptor may be postulated, with mediation of impulses through the antidiuretic hormone of the posterior pituitary. Their observations, when correlated for time of day, confirm the existence of a diurnal rhythm in excretion of electrolyte and, to a certain extent, water. Lewis *et al.* (73) localized the cephalic position of the receptor by applying a sphygmomanometer cuff about the subject's neck and noting the prompt appearance of diuresis when venous congestion was produced. Strauss and co-workers (74) investigated the water diuresis appearing when a recumbent subject was given an infusion of isotonic sodium chloride solution and observed that diuresis did not appear if the subject was in a sitting position. They verified the

findings of Welt and his group, concluding that a pressure receptor and an osmoreceptor were both located in the head.

Leaf & Mamby (75) reported a measurable increase of the antidiuretic activity of dog serum obtained from dehydrated, anemic animals, interpreting this data as evidence for existence of an antidiuretic mechanism not regulated by extracellular fluid tonicity. Henry & Gauer (67) had observed that altering effective circulating blood volume appeared to cause renal adjustment of sodium and water excretion in compensation. Studies of seven dogs subjected to loss of 20 per cent of their theoretical normal blood volume showed that, although blood pressure was unchanged under the experimental conditions obtaining at the termination of this acute hemorrhage, the urine flow dropped to 50 per cent of prehemorrhage control values and then doubled following plasma infusion replacing the volume bled. These investigators point to the associated increase in heart size and lung density after hemorrhage, and a return to normal relationships following plasma infusion. They suggest that possibly thoracic receptors are involved in mediation of these changes in renal function, which possibly also bears some relation to cardiac congestive failure.

Evidence for interaction of adrenal hormones in insuring homeostasis in the field of blood volume is at present fragmentary and inferential for the most part. Barnett and co-workers (76) observed that during amelioration of the nephrotic syndrome following administration of adrenal corticotrophic hormone, increases in plasma volume and glomerular filtration rate to normal levels were associated with the diuresis accompanying remission.

Blood Volume Estimations in Animals

Reynolds (77) reports plasma volume values (T1824) for the cow averaging 39 ± 1.2 ml. per kg. of body weight, blood volume calculated from hematocrit readings being 60 ± 3.0 ml. per kg. Maximum light absorption concentration curves conforming to the Beer-Lambert Law. The dye disappearance curves all corresponded closely to data obtained in the dog and in man.

Sharpe, Culbreth & Klein (78) report an average erythrocyte volume of 2.35 ± 0.18 ml. per 100 gm. of body weight in normal rats, injected with one-half ml. of Fe^{59}-tagged cells. Blood volume calculated from red cell mass and hematocrit readings averaged 4.83 ± 0.31 ml. per 100 gm. body weight. Hansard, Sauberlich & Comar (79) report blood volume values for swine falling within the average range of values for mammalian species, 75 to 85 ml. of blood per kg. of body weight.

Wish, Furth & Storey (80) have made direct estimation of plasma volume, using T1824 or I^{131}-albumin, and of red cell mass, using P^{32} in normal mice. In mice bearing transplanted tumors they injected one-half ml. of tagged material into the tail vein and withdraw one blood sample from the heart 5 to 6 min. after injection. They report values for plasma and red cell volumes in normal mice and in tumor bearing mice developing ovarian

tumors. Increased plasma volume was observed in animals with tumors treated with estrogens. A granulosa cell tumor that secreted estrogens was associated with an increased plasma volume, but a normal red cell mass, while a luteoma that secreted androgens was associated with an increased red cell mass, though plasma volume changed little from normal range. Mice developing ovarian carcinoma had blood volumes lower than normal.

Lewis, Goodman & Shuck (81) analyzed organs of white rats (Wistar strain) for individual organ blood volumes, estimating plasma from T1824 tissue extraction, and red cell mass by hematin content of the same tissue sample. Only the spleen hematocrit was higher than the average venous hematocrit reading, and organ blood volumes given as ml. of blood per gm. of fresh tissue are reported as kidney 0.278 ± 0.038, liver 0.178 ± 0.012, spleen 0.481 ± 0.060, and heart and lungs combined 0.279 ± 0.152. A similar range of values was reported by Kaliss & Pressman (82). Using Fe^{59}, Elmlinger, Huff & Oda (83) found a marked decrease in the reconversion of erythrocyte iron following an experimental increase of normal rat blood volume by transfusion. The major portion of the injected Fe^{59} was located in the liver at necropsy.

Supplee, Hauschilst & Entenman (84) determined plasma volume and plasma protein concentration in rats irradiated with 400, 600, and 750 r. Plasma volume decreased to 80 per cent of normal values in the 750 r group by the third postirradiation day; thereafter, all animals showed an increasing plasma volume, reaching +15 per cent, +47 per cent, and +45 per cent relative to normal values for the respective groups. Plasma protein concentration decreased down to 80 per cent of normal in rats receiving 600r and 750r by the fourteenth day, but total circulating protein, calculated from these data, showed no change at the end of the first week and some increase in all animals in the second week. Cruz, Moussatche & Oliviera (85) studied blood volume changes in dogs following injection of antiplatelet serum, observing decreased blood volume with development of shock. The red cell mass estimated directly from methemoglobin content fell by a proportionately greater amount than plasma volume, measured with T1824.

Everett (86) administered Fe^{59} intraperitoneally to pregnant guinea pigs and observed the radioactivity of the lungs of the newborn. He obtained evidence that the lungs contained considerable Fe^{59} at birth, which increased in the first 5 min. of life and +85 per cent after 7 hr.

Pirozynski & Webster (87) noted a decreased blood volume in rabbits after prolonged exposure to intense cold. Plasma volume fell somewhat lower proportionately than red cell mass. The decrease in both volumes was associated with the appearance of interstitial fluid accumulation in skeletal muscle and trapping of red cells in peripheral vessels. Rodbard, Saiki & Malin (88) investigated body fluid distribution in animals subjected to intense cold or to heat. They employed T1824 plasma volume technique and thiocyanate for estimating interstitial fluid volume. When the animals were placed in the cold environment, both plasma volume and the apparent distri-

bution volume of thiocyanate decreased to 70 per cent of the normal value. In hyperthermia, the plasma volume rose slightly and thiocyanate space rose approximately 10 per cent. D'Amato & Hegnauer (89) studied the plasma and red cell volumes of dogs rendered hypothermic by immersion into an icebath while anesthetized with pentobarbital. The plasma volume measurements with T1824 revealed an average decrease of 13 per cent when the dog's rectal temperature was at 20°C. Red cell mass estimation with P^{32} indicated no significant change in red cell volume.

Observations of Blood Volume Changes in Specific Clinical Conditions

Caton *et al.* (90) studied the circulating red cell volume and the body hematocrit in normal pregnancy and the puerperium using red cells tagged with Fe^{55} for cell volume and the dye method for plasma volume. Twelve women were studied. A significant rise in blood volume was found as early as 160 days before delivery. The whole blood volume increased as much as 45 per cent. The body hematocrit fell 8 per cent and the large vessel hematocrit 15 per cent. The increase in blood volume had diminished to about half the maximum in the first week postpartum but the blood volume took up to 60 days to return to normal. Lowenstein, Pick & Philpot (91) mention the extent of the blood loss in the third stage of labor as 150 to 600 ml. and cite Tysoe, Lowenstein & Simon (92) as having found losses of 810 to 1250 ml. using T1824 measurements.

Berlin *et al.* (93) studied the blood volume in pre-eclampsia as determined with P^{32}-labelled red blood cells. They found a decrease in blood volume in eight pre-eclamptic patients of 26 per cent as compared with normals. The decrease in plasma volume (31 per cent) was greater than the decrease in erythrocyte volume (16 per cent).

Royster and co-workers (94) emphasized the value of blood volume determinations (T1824 method) in radical operations for cancer of the head and neck. They also studied blood losses at operation by weighing sponges promptly after use and measuring the quantity of blood aspirated. The average deficit for preoperative patients with weight loss was 504 ml., and 460 ml. for those not having weight loss. However, individual deficits as high as 1470 ml. were estimated. Correlation was found in patients with carcinoma of the mouth between the duration of the lesion and the amount of the blood volume deficit. At operation, the average blood loss per hr. of operating time ranged from 376 ml. for two patients undergoing radical maxillary resection, to 770 ml. for four patients undergoing jaw-tongue-neck dissection. The largest loss per operation occurred in seven patients undergoing jaw-neck dissection with an average total loss of 4068 ml. per patient (average operating time 4.3 hr.). In an illustrative case, losing 2950 ml. at operation or as drainage in the first four postoperative days, 1750 ml. was replaced by transfusion, leaving a theoretical decrease of 1200 ml. The measured decrease as determined by the T1824 method was 850 ml., leaving unaccounted a discrep-

ancy of only 350 ml. This paper is representative of the use which has been made clinically of blood volume data. Finley *et al.* (95) call attention to the loss of plasma with a rise in hematocrit in the first 24 hr. after major intrathoracic operations. Walker (39) has estimated blood volume deficits before operation in a series of patients admitted to a general surgical service for gastric resection and found a mean deficit of about 1000 ml. In a series of patients with colon carcinoma he found mean deficits of about 800 ml.

Bosch *et al.* (96) comment on the value of preoperative blood volume determinations in the elderly surgical patient and McInnes, Bodansky & Brunschwig (97) also point to their usefulness in patients undergoing radical surgery. Other papers on clinical evaluation have appeared (98, 99, 100). Parsons, Williams & Forsythe (101) emphasized especially the continuing need for blood in the postoperative period following extensive operations. Further study of blood loss during operations was made by Saltzstein & Linkner (102) in a consecutive series of 212 surgical operations with the following results—appendectomy, hernia, thyroidectomy, and cholecystectomy: 200 ml.; hysterectomy, colon resection, gastric resection: 300 to 1000 ml.; radical breast amputation, abdominoperineal resection, combined neck and jaw resections: over 1000 ml.

Reeve (103) has studied the relation of the effects of trauma on blood volume and the symptoms caused by reduced blood volume. He notes that reductions to below 80 per cent of predicted normal are accompanied by decreased ability to withstand stress, such as operation, and that decreases to 70 per cent or below cause a decline in arterial pressure and the heart is unable to pump enough blood to the tissues. He notes that plasma substitutes should play a useful role in such situations but that transfused patients do not increase their plasma volumes much above 1.3 times the preinjury value and, therefore, if they have lost large quantities of cells by hemorrhage, their blood volumes persist at low levels.

Grant & Reeve (104) have attempted to correlate wound size with blood loss. A very wide scatter of values was found but their charts demonstrate some tendency to correlation, as might be expected. Their study of quantitative factors associated with major trauma is one of the most thorough to appear. The blood loss was estimated by subtracting determinations made with the T1824 method from theoretical normals. In the "very large wounds" (over five hands in comparable area), 6 out of 10 patients showed losses of 60 per cent of whole blood volumes. The mean for the "large wounds" (three to five hands) was of the order of 40 per cent, for the "moderate wounds" (one to three hands) widely scattered but with nearly half the values below 30 per cent loss, and for the "small wounds" (less than one hand) again scattered but 8 of 14 cases showed losses of 5 per cent or less.

The value of intra-arterial transfusion has been discussed by Seeley (105). The value of this route would appear to rest on the supposition that by directly filling the arterial side of the circulation, the flow through vessels to vital areas such as the coronary arteries is increased, whereas, if the same

amount of blood were given by vein, it would not raise the blood pressure until it passed through the heart. While this advantage may seem rather marginal, Seeley states

> where profound shock occurs and the disparity between vascular volume and vascular tree capacity cannot be estimated, rapid transfusion by the arterial route is highly effective in bringing about resuscitation and maintaining a blood pressure at any desired level, except in cases of continuing massive hemorrhage or very late irreversible shock.

In rheumatoid arthritis, Garry (106) has pointed out that the red cell mass is usually reduced about 25 per cent and that restoration of this deficit by transfusion usually results in subjective improvement.

The Alteration of Blood Volume by Infusions of Colloidal Solutions

The experience of World War II intensified the appreciation of surgeons of the very important role played by blood volume in the body economy. It also served to emphasize that, while plasma replacement could be a life saving measure, replacement of the erythrocytes had to be accomplished before patients who had suffered severe hemorrhage reacted as good risks during subsequent surgical procedures. Since World War II, realization that the atom bomb injuries might cause a tremendous increase in the requirements for supplements to the plasma volume has led to an intensification of research on so-called plasma volume expanders or plasma extenders (i.e., on artificial substances with colloidal properties suitable for use in the circulation and devoid of toxic properties).

Ossein gelatin, skin gelatin, dextran, and PVP[2] were developed during World War II and used to some extent in various countries. During the period under review, additional studies have been carried out on these materials, and newer preparations including oxypolygelatin, modified fluid gelatin, and polyglucose have been studied. In addition, certain derivatives of human plasma, notably modified globin and the stable plasma protein solution have been studied. Certain of these studies have been directed at problems of toxicity and others at the problem of effectiveness.

Three papers from the Mayo Clinic attest to the clinical usefulness of dextran, periston (PVP)[2], and gelatin in supportive therapy (107, 108, 109). Hehre & Neill (110) and Hehre & Sugg (111) reported extensive studies on the serological activities of dextran, calling attention to certain cross sensitization reactions between dextran and certain strains of pneumococci. Kabat & Berg (112) called attention to the production of precipitins and cutaneous sensitivity in man by injection of small amounts of dextran.

Von Frijtag Drabbe & associates (113) have examined patients for changes in liver function following dextran, PVP and oxypolygelatin and find none which they consider of clinical significance. PVP alters the response to the phenol used as a reagent in determining lipid. This is an *in vitro*

reaction and these authors have adapted it for the determination of the PVP concentration in plasma and urine (114). Renal function tests have been variously affected by dextran. Fleming, Cargill & Bloom (115) report no adverse effects on clearance studies in 10 human subjects receiving from 500 to 1500 ml. of 6 per cent dextran. Froeb *et al.* (116), studying dogs, found a drop in Tm_{PAH}[2] after dextran. Michie (117) reported a significant diminution in Tm_{PAH} in three of four patients with prior renal damage and at least one additional patient without prior renal damage. Other tests were unimpaired and effective renal plasma flow was often increased. Michie's patients received 1000 ml. of 6 per cent dextran daily for six days.

Tests for the effectiveness of dextran have been carried out by Witham, Fleming & Bloom (118) on the effect of cardiac output and other circulatory dynamics showed that 500 ml. of 6 per cent dextran, given at a rate of 25 ml per min. in five human subjects, caused little change in systemic arterial pressure or pulse. However, the pulmonary artery pressure increase was prolonged, cardiac output was increased, and it was estimated that there was an increase of 98 per cent in right ventricular work and of 41 per cent in left ventricular work. Bloom (119) has summarized some of the studies on this subject in a review article. Pulaski (120) tested the effect of dextran (Macrodex) in reducing the mortality in hemorrhagic shock in rabbits. In a dose of 30 ml. per kg. the mortality was reduced from a control level of 90 per cent to 20 per cent. This compares with 50 per cent for 0.9 per cent NaCl, 12 per cent for plasma, and 6 per cent for oxypolygelatin. On the basis of a pattern of repeated hemorrhages, he rated the substances he tested in the following order: plasma > oxypolygelatin > dextran > 0.9 per cent saline.

Parkins, Perlmutt & Vars (121) compared the effectiveness of the various expanders in hemorrhagic shock. According to their technique, dogs were bled at 4 ml. per kg. per min. to an arterial pressure end point of 20 mm. Hg and immediately reinfused with the solution to be tested at 4 ml. per kg. per min. until a volume equal to the volume removed had been withdrawn. After 3 hr., and in some cases at 6, 12, or 24 hr., the animal was bled again and the amount of blood withdrawn to lower the blood pressure to 20 mm. Hg compared with the original bleeding. This ratio called the "Bleeding Volume Index" was 96 per cent for whole blood, 87 per cent for dextran (6 per cent), 83 per cent for modified fluid gelatin (3 per cent), 81 per cent for oxypolygelatin (5 per cent and 6 per cent), 54 per cent for 0.9 per cent NaCl. Because of the idiosyncrasy of dogs for PVP[2], comparable figures could not be obtained. These authors ran similar experiments substituting an hour of hypotension at arterial pressure of 30 mm. Hg for the initial hemorrhage to blood pressure of 20 mm. Hg. In this series, whole blood gave a B.V.I. of 58 per cent, 53 per cent for dextran, 63 per cent for modified fluid gelatin, 33 per cent for oxypolygelatin, 12 per cent for 0.9 per cent NaCl.

Renal function studies have been carried out with PVP by Barker (122), and with modified fluid gelatin and oxypolygelatin by Michie (123) in pa-

tients with no deleterious effects on glomerular filtration rate, effective renal plasma flow, or Tm_{PAH}.[2] Wallenius (124) reported the relief of nephrotic edema by dextran infusions.

All of the work on dextran and PVP[2] has been done against an extensive background of earlier work in Europe where thousands of liters of dextran have been used in Sweden and many thousands of liters of PVP have been used in Germany. Bull *et al.* (125) review the British experience with dextran and much of the Scandinavian experience is covered by Thorsen (126). Marshall and co-workers (127) studied blood changes in normal dogs during chronic blood volume expansion with dextran. No histologic changes were found after 10 to 20 ml. of dextran 6 per cent, three times a week for 13 weeks. The hematocrit was lowered. Tissue changes have been studied by Hartman (128) and by Nelson & Lusky (129), among others.

Burn shock has been studied chiefly in rodents. None of the plasma expanders thus far have been demonstrated to have any advantage over electrolyte solutions in appropriate dosage in these species [McCarthy (130), Millican *et al.* (131)]. The latter authors also employed plasma expanders to treat tourniquet shock with equally negative results. Rosenqvist (132) has reported good clinical results with the use of dextran after burns, as has Evans (133). It seems fair to conclude on the basis of the bulk of the evidence that these agents, when properly prepared, are effective in causing abatement of the symptoms of shock and that they are sufficiently nontoxic to permit emergency use when nothing better is available. Recent attempts have been made to determine more precisely their effect on blood volume. Most authors have used a plasma volume rather than a cell volume technique in as much as these materials are substitutes for plasma rather than whole blood. The two methods used most have been the dye method with T1824 and the I^{131} method using albumin tagged with I^{131}.

A basic consideration in following the persistence of these materials in the bloodstream and the persistence of the plasma volume increase which they produce is whether to give them to normovolemic subjects, or to plan the experiments so that the subject will be normovolemic at the end of the infusion. There is evidence in earlier literature that plasma infusions disappear from the circulation fairly rapidly if added to a normal circulation. Seavers & Price (134) found the volume increases following whole blood transfusion in the dog to be transient. Therefore, Elder, Barker & Walker (135) tested these materials in subjects from whom 1000 ml. of blood were removed before giving 1000 ml. of the material to be tested. On this basis, oxypolygelatin yielded a volume replacement that remained substantially intact for 12 hr., although only 25 per cent of the oxypolygelatin was measurable at 12 hr. [Barker *et al.* (136)]. It apparently remained long enough to be replaced by native plasma protein, thus maintaining the total plasma volume.

In subsequent studies, Elder and associates (137) obtained the figures

given in Table I for volume retention at 4 hr. and 12 hr. in bled and unbled human subjects.

TABLE I

COMPARISON OF MAINTAINED PLASMA VOLUME IN BLED VERSUS UNBLED NORMAL VOLUNTEERS

	Percentage of Volume Retained: At 4 hr.	At 12 hr.
Fluid gelatin after bleeding	91	88
Fluid gelatin without bleeding	23	4

There were four subjects in each series. These data would imply that studies of volume retention in normovolemic individuals were not likely to be of much value. Analysis of the plasma for the modified fluid gelatin content indicated that the rate of disappearance of this expander was not far different in the two series but that, in the unbled, plasma protein left the circulation and, in the bled subjects, it came into the circulation.

The same workers obtained volume retention data at 12 hr. on bled subjects as shown in Table II.

TABLE II

PERCENTAGE RETENTION OF VOLUME INFUSED

Material Tested	Percentage of Initial Volume
Plasma	100
0.9 per cent NaCl solution	57*
Oxypolygelatin	82
Modified fluid gelatin	91

* Based on 3 of 4 subjects. The fourth subject had to have his blood back before the twelfth hour.

In terms of the expander in grams, retention was lower as shown in Table III.

TABLE III

PERCENTAGE OF INFUSED SUBSTANCE RETAINED

Material Tested	Percentage of Original Weight At 15 min.	At 4 hr.	At 12 hr.
Oxypolygelatin	66	34	25
Modified fluid gelatin	89	61	40

In summarizing this field, it is impossible not to point to the difficulty of stating what the ideal plasma volume expander should do. It should be nontoxic. It should be nonantigenic and nonpyrogenic. It should stay in the body long enough but not too long. No precise definition has been made of how

long this is, however, 50 per cent at 12 hr. has been proposed and is probably a reasonable figure. As long as it will remain long enough to permit the native plasma protein concentration to be returned to normal, the expander should be highly satisfactory. It is evident from plasmapheresis experiments that the homeostasis of plasma protein will be impaired by malnutrition and it could well be that, in a malnourished population, a relatively long lasting expander would be desirable.

Under present conditions, PVP[2] 3½ per cent (up to 3 l. per person), dextran 6 per cent, oxypolygelatin 5 per cent, modified fluid gelatin 3 per cent, appear satisfactory. The last two have not received as wide clinical trial as the two former They are closely related to ossein gelatin which has had considerable use and has been very satisfactory, except that the high gel point of ossein gelatin necessitates its being warmed before use.

Added to the numerous substances already proposed as plasma volume expanders is "plantago," prepared from the mucilage *Plantago psyllium* which was reported by Behrman & Hartman (138). Moderate storage in the body was found for 7 to 10 days after infusion but no chronic retention. The solution tested was not as effective as pectin in hemorrhagic shock in dogs. Extensive studies have been made on a number of other blood derivatives such as albumin, modified globin, hemoglobin, and stable plasma protein solution, and also on the use of certain other substances not derived from human blood. Most of this work is beyond the scope of this review. The possible usefulness of crystalloid solutions in replacement therapy after experimental hemorrhage and burns has received considerable attention. Few precise measurements of blood or plasma volume have been made in this field but the effects on arterial pressure, hematocrit, and survival have been studied, and the implications are strong that, when large enough amounts of such solutions are used, some improvement in blood volume results. Parkins, Perlmutt & Stait (139) have shown that 0.9 per cent NaCl solution, when given as an immediate replacement for hemorrhage, is quite effective in the dog if given in an amount equal to two or three times the blood volume removed. McCarthy (140) has shown that hypertonic crystalloid solutions such as 1.4 per cent NaCl in large volumes (18 per cent of body weight) are desirable in the severely burned rat in promoting 10 day survival.

Additional Recent Contributions on the Subject

Unfortunately, the space available for this review does not permit an adequate consideration of many excellent papers that have appeared during the two years ending July 1st, 1952. Among these are additional papers on methods such as that by Armin *et al.* (141) in which simultaneous determinations of blood volume were made in 29 rabbits by the T1824 method and the P^{32} method. Auerswald (142) reported data on 53 human subjects in which he found an average plasma volume of 41 ml. per kg. Aust and coworkers (143) proposed a rapid method for clinical blood volume determination using I^{131} which they had tried in 40 cases. In eight patients determi-

nations with T1824 had been run simultaneously and in some the agreement was good though, in others, there were discrepancies up to 20 per cent.

Bianca (144) estimated blood volume during the administration of an epinephrine-like drug which mobilized depot red blood cells to a varying degree in different species. In the horse, this mobilization of cells amounted to 11.6 per cent, whereas, in certain other species such as the sheep, it was about half of this figure. Lewis & Goodman (145) made a study of the excretion kinetics of T1824 and concluded that in the rabbit there was no significant difference between plasma volumes obtained from calculations based on linear and exponential extrapolation. McLain, Ruhe & Kruse (146) also did concurrent estimates of blood volume by a bleeding method and dye methods in rabbits and dogs. They felt that the bleeding method gave the most consistent results; 62 ml. per kg. in dogs and 43 ml. per kg. in rabbits. Montgomery (147) reported a method of determining blood volume of the rat using radioactive phosphorus. The average blood volume in 34 adult white rats was 6.3 per cent of the body weight. Von Porat (148) reported on the use of an iron-carbohydrate complex and T1824 in the determination of blood volume.

Remmer (149) made a study of sources of error in blood volume estimation. An additional study of blood volume in the living organism was reported by Schotten (150). A careful study of the P^{32} method was made by Schwaiger & Schmeiser (151) who found it more than accurate enough for clinical purposes. Shapiro (152) reported a technical modification of the T1824 method and Storaasli *et al.* (153) made a detailed comparison of the T1824 method, the P^{32} method, and the radioactive iodinated-albumin method, in 10 dogs. Except in one instance, the results with the T1824 method gave slightly higher values. Surtshin & Rolf (154) studied dye concentration curves following two successive injections of T1824 and found that multiple doses were satisfactory in the dog, in the rabbit, and in man. Yalow & Berson (155) used radioactive potassium (K^{42}) to tag erythrocytes for blood volume determinations. They reported results which were very close to those obtained with P^{32} and believe that radioactive potassium was advantageous because it is a strong beta and gamma emitter.

Chaudhuri & Chakravarti & Dutta (156) reported a study of the blood volume in healthy Indians. In 50 subjects they found a mean plasma volume of 47.7 ml. and blood volume of 83.1 ml. per kg. using the T1824 method. Steinbeck (157) reported studies on 32 Australian males with T1824 and found a mean plasma volume of 47.44 ml. per kg.

Many studies have been directed toward the use of blood volume methods in various clinical conditions. Agress *et al.* (158) studied 32 cases of myocardial infarction. Blood volume in those developing moderate to severe shock, was 72 to 73 ml. per kg. as compared with 84 ml. per kg. in the nonshock group. Furthermore, after convalescence those patients who had been in shock showed a deficit, whereas those who had not been in shock did not.

Agress and co-workers (159) reported an experimental study of myocardial infarction in dogs and found a 20 per cent loss of blood volume in 5 hr. as compared with controls. Aquilina & Butsch (160) studied, by means of the T1824 method, 20 surgical patients undergoing gastrectomy. During the postoperative period 10 patients were given fluids containing 11 gm. of salt per day, and 10 other patients received no salt. The group receiving salt were shown to be better off with respect to plasma volume, red cell volume, and total circulating plasma protein. Baez, Villasenor, & Fierro (161) determined blood volume in 50 patients with proved cirrhosis of the liver. The plasma volume was increased from 25 to 61 per cent and seemed highest in those with high portal pressures. Total blood volume was in general about normal. Bateman (162) studied blood volume of 33 patients with cancer, 8 patients with arrested cancer, and 10 controls who were believed free of cancer. The blood volume was variable and seemed to bear no direct relationship to the cancer. A decrease was found in three patients with impaired alimentation.

Berlin *et al.* (163) studied blood volume in pre-eclampsia by the P^{32} method in eight patients and found a marked reduction in blood volume with about twice as great a reduction in plasma volume as in cell volume. Berlin and co-workers (164) studied blood volume in 26 patients with pulmonary tuberculosis. On the average, blood volume was low, though two had elevated blood volumes which the authors believed were associated with secondary polycythemia. Mean figures were 53.5 ml. per kg. in females as compared with 64.4 in the normal control series. In males the figures were 60.58 for the tuberculous patients as compared with 67.6 ml. per kg. in the 71 normal males. Berlin *et al.* (165) reported on the blood volume of 32 normal women as measured with P^{32}-labelled red cells. The mean blood volume was 64.4 ml. per kg. with a red cell volume of about 27 ml. per kg. Berlin, Lawrence & Gartland (166) studied the blood volume in chronic leukemia and found that in 24 patients with chronic lymphatic leukemia 80 per cent were in the normal range, 12 per cent were low, and 8 per cent were high. Of 13 patients with chronic myelogenous leukemia, 11 showed high values. Berlin, Lawrence & Gartland (167) also studied blood volume in polycythemia. In 53 cases of polycythemia vera, 30 of the 32 cases whose hematocrits exceeded 55 had high red cell volumes; 22 had low plasma volumes. Six cases of secondary polycythemia had high red cell volumes with low plasma volumes and seven cases of relative polycythemia had normal red cell volumes and low plasma volumes.

Coryn (168) reported on the clinical use of the radioactive phosphorus method and endorsed its clinical value. Daum (169) made a study of plasma and blood volumes in hyperthyreosis and myxedema. The value of blood and plasma volume studies in the severely injured was attested by Dodds & Curry (170). Faugere & Maillet (171) used a 25 per cent solution of PVP^{32} to determine plasma volume in pregnancy and found very large increases.

Nicholson & Jensen (172), using the T1824 method, encountered decreased blood volume in surgical patients, and particularly discussed its role in 40 cases of wound dehiscence.

Karlberg & Lind (173) studied blood volume in the newborn and obtained high figures of the order of 100 ml. per kg. with rather a wide spread (70 to 150). Mallet-Guy, Devic & Graugeon (174) report 400 determinations in 216 surgical cases and believe that the blood volume method is the only way in which intravenous therapy can properly be gauged. Mollison, Veall & Cutbush (175) studied red cell and plasma volume in newborn infants using T1824 and P^{32}-tagged red cells and occasionally the Ashby technique. Fifty-three children were studied. The average normal plasma volume was given as 41.3 ml. per kg. in 34 children and the total blood volume as 84.7 ml. per kg. in 28 children. They found the whole blood hematocrit bore a fairly constant relationship to the venous hematocrit over a fairly wide range. This ratio was 0.87.

Morton, Siegel & Schulte (176) reported blood volume deficits in patients with carcinoma of the colon. The average blood volume was given as 81.8 per cent of normal for 25 cases and the average red cell volume was 69.8 per cent.

Murphy (177) reported the effect of a rice diet on plasma volume and found a highly significant decrease in the plasma volume in a 14 week period. There was no simple relationship between chemical and clinical results. Nelson & Lindem (178) studied 17 patients with traumatic injuries, most of whom had lost weight after sustaining their trauma. Blood volume deficits ranged from 4 to 26 per cent. Von Porat (179) made an extensive study of blood volume methods and in particular studied blood volumes in patients with tuberculosis. In 25 men with pulmonary tuberculosis, there was an average decrease in blood volume of 900 ml. and in 20 women an average decrease of 300 ml. Reissman (180) studied the blood volume in dogs during altitude acclimatization at 20,000 feet. Plasma volume decreased to 75 per cent, red cell volume rose to 170 per cent; blood volume was 125 per cent of the ground value. These changes required about five weeks.

Blood volumes in normal and burned dogs were studied by Salzberg & Evans (181) by the P^{32} method and by the T1824 method. Evans' standard 20 per cent burn was used, with pentobarbital anesthesia. The plasma loss amounted to 28 per cent. The average ratio of the P^{32} red cell volumes to the T1824 red cell volumes was 0.98 in normals, but only 0.73 in animals 6 hr. after the burn. The P^{32} studies showed an 11 per cent loss in red cell volume in the first 6 hr. Scott, Elliott & Clay (182) carried out blood volume determinations in congenital cyanotic heart disease, making simultaneous measurements with Evans blue and P^{32}. They found that cyanotic individuals have a diminished plasma volume and a greatly increased red cell volume, with a net increase in blood volume. Storey, Wish & Furth (183) studied changes in cell and plasma volumes produced by total body x-radia-

tion in rabbits. After 1000 r total body irradiation, a large drop in red cell volume occurred from the third to the seventeenth day followed by slow recovery. The plasma volume dropped slightly then rose above normal, but blood volume did not reach normal within 23 days. Similar responses were found in mice receiving 575 r total body irradiation.

Sutton (184) employed P^{32} to study the effect of *l*-norepinephrine upon corpuscular volume and hematocrit and found that this vasoconstrictor drug caused a moderate elevation of the large vein hematocrit in five of seven individuals. Tauret & Glandard-Arragon (185) have found an 18 to 30 per cent decrease in plasma volume in cirrhosis and an 8 to 15 per cent decrease in infectious jaundice. They found the plasma volume was usually normal when obstructive jaundice was caused by gall stones. However, of 10 patients with carcinoma of the pancreas, the average plasma volume decrease in this group was 20 per cent. Tennant *et al.* (186) found blood volume methods practical and useful in the clinical management of intravenous therapy. Tysoe, Lowenstein & Simon (187) studied blood volume during pregnancy and the puerperium and published an extensive review with a great deal of data similar to some of that mentioned earlier in this review. Villasenor (188) studied normal blood volumes in Mexican men and women and obtained figures of 83.45 ml. per kg. for 21 men between the ages of 19 and 40 years, and of 84 ml. per kg. for 21 women between 17 and 38 years. Warren & Elkin (189) studied blood volume in 41 patients with arteriovenous fistulas. In 56 per cent there was no significant change after closure of the fistula, but in 44 per cent there was a decrease in plasma volume, ranging from 200 ml. to as high as 1060 ml. per sq. m. of body surface. They believe that in these individuals, the plasma volume had become abnormally increased during the presence of the fistula.

Additional papers deserving of mention include that by Reich and Howard (190), who used the sternal route in measuring blood volume and found that it gave almost identical results with those obtained on venous blood. Price (191) reviewed the subject of blood volume in health and disease and stated that good pre and postoperative care included control of blood volume. Extensive valuable blood volume data are found in the excellent monograph by Moore & Ball (192). Kjellberg *et al.* (193) carried out extensive studies on the relationship of blood volume to pulse frequency and the filling rate of the left ventricle upon standing. A number of blood volume studies are included in the monograph by Hardy (194) on surgery and the endocrine system, although the work is not directed primarily toward the study of blood volume.

Gregersen & Nickerson (195) studied the relationship of blood volume and cardiac output to body type in a series of normal young men. Mean plasma volume for the intermediate types was 45.6 ml. per kg. as compared with 40.5 ml. per kg. for endomorphs, 50.1 ml. per kg. for ectomorphs, and 56.5 ml. per kg. for extreme ectomorphs. They felt that these differences

helped to explain some of the differences encountered in the literature. Gilbert & Lewis (196) studied the effect of exercise on plasma volume in patients with heart failure. During exercise, a transitory rise in peripheral venous pressure accompanied by a roughly proportionate decrease in plasma volume was found. These authors used the T1824 method. Cizek & Zucker (197) studied the effect of hypoproteinemia produced by plasmapheresis on plasma and interstitial fluid volumes and renal clearances of dogs. These animals had a normal diet and in the four dogs studied, three maintained a normal plasma volume and one an increased plasma volume in spite of the fact that the average colloid osmotic pressure was reduced to 10.7 mm. Hg. Finally, attention is called to the section on blood volume in the splendid review on shock and burns by Everett I. Evans (198).

The two year period under review reveals extensive activity in the study of blood volume and in the application of basic knowledge, both to clinical problems and to further basic research. The progress that has been made is not only of great potential value in clinical medicine but it points the way to further research, the results of which promise to be of increasing importance in physiology, in medicine and surgery, and in certain of the specific problems of civil defense.

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BLOOD: FORMED ELEMENTS[1]

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Since this review attempts to cover material under the scope of the above title for the four-year period from approximately July 1948 to July 1952, space limitations have necessitated omission of material dealing with bone marrow physiology, hemoglobin and iron metabolism, immunohematology, and chemotherapy of blood dyscrasias. The authors have emphasized those aspects of the field in which there were new developments or in which several related contributions were made. A major event in biology was the publication of the first portion of the *Biological Handbook* which includes hematological values for many animal species and man (1). In line with the interests of the reviewers, much of the material presented is concerned with nutritional and hormonal influences on blood cells.

Investigations Using Newer Methods in Hematology

Physical methods.—Reports have appeared on the use of the electron microscope [Rebuck (2); Bessis (3)], the phase-contrast microscope [Moeschlin (4); Discombe (5); von Lüdin (6)] and the ultraviolet microscope [Thorell (7)] as tools for expanding our knowledge of the morphology and physiology of blood cells. Satisfactory methods have been developed for making radioautographs of individual blood cells [Morse (8)] and for separation of formed elements of the blood [Buckley *et al.* (9)].

Chemical methods.—Pearse (10) reviewed modern histochemical methods, and Valentine (11) summarized and evaluated biochemical studies on leukocytes. Code (12) has thoroughly reviewed methods of determination of blood histamine, its cellular distribution, and causes for its release from cells. Valentine *et al.* (13) also reviewed the literature on blood histamine with particular reference to alterations found in diseases involving leukocytes. Granulocytes are the main source of blood histamine in most species. There is, however, no correlation between histamine content and number of granulocytes in the blood. Eckert & Tötterman (14) confirmed the finding of previous investigators that histamine is not an essential part of the eosinophil granule. Graham *et al.* (15) found by the use of microtechniques that the blood basophil contains at least 50 times the amount of histamine found in any other blood cell. They believe that this finding may explain the extremely high values of blood histamine seen in chronic myelocytic leukemia

[1] The following abbreviations are used in this review: PGA (pteroylglutamic acid); ACTH (adrenocorticotropin); DCA (desoxycorticosterone acetate); S Hgb (hemoglobin of sickle cell anemia); N Hgb (hemoglobin of normal individuals); ACE (adrenal cortical extract).

since this is one of the few conditions in which large numbers of basophils are found in the blood. Shimkin and associates (16) reported altered histamine levels in leukemia and erythremia. They also found a rough parallel between the white count and histamine level in chronic myelocytic leukemia. They do not believe, however, that the histamine is physiologically active and can offer no explanation for the increased amount.

Wachstein (17), in a study of the distribution of histochemically demonstrable glycogen in human blood and bone marrow cells, found a positive reaction in the cytoplasm of megakaryocytes and platelets as well as myeloid cells. The intensity of the staining process increases with the maturity of the cells. Gibb & Stowell (18) found a similar distribution of glycogen in human blood cells and stated that the only cells not staining for glycogen are the large cells of infectious mononucleosis. They observed no alteration in cellular glycogen in any disease state with the possible exception of polycythemia in which there was a suggestive increase.

Bloom & Wislocki (19), using a new and more specific histochemical method for lipid, found this substance in the granules of all cells of the granulocytic series. The amount in eosinophil granules was variable. Many eosinophils have granules composed of protein surrounded by phospholipid.

A variety of enzymes are found in abnormal concentration in various hematological diseases. Kerppola (20) reported an abnormal distribution and concentration of acid and alkaline phosphatase in anemia and leukemia. Valentine & Beck (21) and Beck & Valentine (22) have thoroughly studied the phosphatase activity of leukocytes in health and disease and believe that the abnormal patterns seen in disease states such as leukemia and erythremia may have diagnostic as well as prognostic significance. Anlyan and coworkers (23) observed altered values of β-glucuronidase activity of the white cells in leukemia and Hodgkin's disease. Contopoulas & Anderson (24) found a high cellular content of sulfhydryl components in leukemia. Sabine (25) and Scudamore *et al.* (26) reported that cholinesterase concentration is altered in the red cells in anemia. The granules of leukocytes were studied by enzymatic techniques by Laves & Thoma (27). They found a significant difference in the chemical structure of blood cell granules of different species.

The majority of the above studies are still in the descriptive stage so that the role of these substances in cellular metabolism and the significance of altered values in disease are yet to be elucidated.

Immunocytological methods.—It is now well established by the use of several techniques that the mature lymphocytes of the blood of immunized animals both contain and produce antibody. Keuning & van der Slikke (28) extracted antibody from lymphocytes, and Wesslen (29) found the that blood lymphocytes produce antibody in tissue culture. Wesslen (29) in animals and Lawrence (30) in man presented indirect evidence that lymphocytes of the blood contain antibody since these cells are the only leukocytes that passively transfer the antibody for the tuberculin response. Godlowski (31) presented evidence that eosinophils contain antigens.

Dougherty & Schneebeli (32) using a quantitative technique provided further experimental evidence that blood lymphocytes are a principal source of macrophages. This phenomenon depends, in the opinion of most workers, on a transition from lymphocyte to a phagocytic form. Seitzer & Sandkülher (33), however, presented evidence that blood lymphocytes phagocytize when conditions of extreme bacteremia exist.

The Erythrocyte Series

Vitamin B_{12}, pteroylglutamic acid, and related substances.—The interrelationships of factors that influence the megaloblastic anemias, and thus are important in normal erythropoiesis, have been most ably summarized and critically analyzed by Girdwood (34). He states that the experimental evidence to date indicates that PGA[1], vitamin B_{12}, and the citrovorum factor are all concerned in methyl metabolism as well as in the metabolism of glycine, serine, ethanolamine, and formic acid, all of which are probably concerned with the synthesis of purines, pyrimidines, and porphyrins. Just where these substances fit into the metabolic cycle is not known, although several theories have been advanced on the basis of bacterial, animal, and human studies. One theory is that vitamin B_{12} acts merely by releasing PGA from its conjugates; another states that PGA has a "mass action" effect in pernicious anemia and that traces of vitamin B_{12} are used up in this process. This latter theory, elaborated by Vilter *et al.* (35) and based mainly on bacterial studies, proposes that folic acid is concerned with the formation of purines and pyrimidines, such as thymine, and that vitamin B_{12} is concerned with the formation of ribosides, such as thymidine, from these purines and pyrimidines. Thus, these substances act at different points along the chemical chain reaction leading to the formation of nucleic acids.

There seems to be an agreement that vitamin B_{12} is identical with the extrinsic factor and possibly also is the antianemic liver principle of Castle [Berk *et al.* (36); Callender & Lajtha (37)]. The latter authors found that vitamin B_{12} when mixed with gastric juice (intrinsic factor) forms a thermolabile hematopoietic factor which ripens megaloblasts *in vitro*. However, they found also that vitamin B_{12} given parenterally to pernicious anemia patients appears in the serum as active hematopoietic principle, which suggested to them that there is an extragastric source of intrinsic factor. This is in line with the findings of Berk *et al.* (36) that vitamin B_{12} although effective parenterally is more effective if incubated with gastric juice.

Horrigan *et al.* (38) have established a direct action of vitamin B_{12} on megaloblasts by instilling this compound into the human marrow cavity and observing maturation of megaloblasts and correction of abnormalities in cellular nucleic acid metabolism. Folic acid (PGA) given the same way has no such action although it does if given parenterally. They conclude that probably the latter compound has to be converted into an active hematopoietic substance by enzymatic activity elsewhere in the body. Thompson (39) tested the action of these compounds on megaloblasts in marrow culture

and found the reverse, i.e., satisfactory maturation with folic acid but not with vitamin B_{12}, liver, or thymine. One explanation for this discrepancy is that vitamin B_{12} is only active in bound form and that binding does not occur *in vitro* [Horrigan & Heinle (40)].

The relationship of citrovorum factor, an essential growth factor for *Leuconostoc citrovorum* [Sauberlich & Baumann (41)], and folinic acid factor [Bond *et al.* (42)] to each other and to folic acid are subjects of intense investigation. It appears that these two compounds are similar and from the results of animal experiments appear to be more metabolically active than folic acid itself [Nichol & Welch (43); Dietrich *et al.* (44); Goldin *et al.* (45)]. Citrovorum factor is also reported to be effective in maturing megaloblasts in marrow culture [Callender & Lathja (46)]. Nichol & Welch (43), using rat liver, found that ascorbic acid accelerates the conversion of folic acid to citrovorum factor. Hill & Scott (47) confirmed this finding, using chick liver. They suggest that ascorbic acid could be acting in this manner merely by virtue of its reducing properties. This may be the mechanism of the effect of ascorbic acid in the experimental megaloblastic anemia of monkeys and nutritional megaloblastic anemias of infants which can be cured by ascorbic acid alone, or by PGA, or folinic acid without ascorbic acid [May *et al.* (48, 49)].

Attempts to reproduce the entire picture of pernicious anemia in experimental animals have not been successful. The closest approach was the production of a macrocytic anemia in swine fed a diet lacking PGA and poor in vitamin B_{12} [Cartwright *et al.* (50)]. No true megaloblasts were found in the bone marrow although megaloblast-like cells were produced. When a diet deficient in vitamin B_{12} alone was fed to swine, a mild to moderate normocytic type of anemia developed which, curiously enough, did not respond to vitamin B_{12} [Cartwright *et al.* (51)]. These investigators suggest that either the B_{12} deficiency that was produced was not severe enough or that PGA may prevent the development of a megaloblastic anemia even in the absence of B_{12}. Johnson *et al.* (52), using the baby pig, found that folic acid deficiency produced more abnormal appearing nucleated red cells than did B_{12} deficiency.

Hormonal effects.—The relationship of the endocrine glands to erythropoiesis is less well established than that of the vitamins. No direct role has been found for any hormone although hormones of the hypophysis, gonads, adrenal, and thyroid have been implicated. The mechanism of the anemia which follows hypophysectomy has been reinvestigated in rats by Berlin *et al.* (53), who found a 55 per cent decrease in total red cell volume following the operation. They state that their evidence is not conclusive as to whether such a decrease is the result of reduced red cell production, increased rate of removal, or both. Feigin & Gordon (54) found that hypophysectomized rats did not respond with the usual rise in red cells when subjected to moderate barometric pressures. Higher pressures, however, produced erythrocytoses in hypophysectomized animals.

Silbergleit (55) found that, whereas intact and sham operated rats recover completely from hemorrhagic anemia within 10 days, bled hypophysectomized animals show only a partial recovery at this time. The red cell count at 10 days is at the maximum level reached following the bleeding and is equivalent to the number of red cells characteristically found in unbled hypophysectomized animals. Incomplete regeneration was ascribed to the lower level of metabolism following hypophysectomy. Nelson (56) did not find that adrenalectomy caused any impairment in erythrocyte regeneration following hemorrhage as both intact and operated rats attained their prehemorrhage levels in the same length of time.

Whether growth hormone of the hypophysis regulates red cells was tested by Gaebler & Mathies (57) who conclude on the basis of their data that lack of this hormone is not an important factor in the anemia of hypophysectomy.

There is considerable evidence supporting the earlier suggestion of White & Dougherty (58) that adrenocortical secretions enhance erythropoiesis. Garcia *et al.* (59) reported that the usual drop in red cell volume in rats after hypophysectomy can be prevented by ACTH.[1] These authors find that 116 days of ACTH treatment of intact animals results in an increase of red cell volume of approximately 1.3 times that of controls. Piliero *et al.* (60) studied the marrow of rats made anemic by adrenalectomy and observed an increased percentage of myeloid cells with a "shift to the left" and a decreased percentage of developing red cells. Adrenal cortical extract prevented the anemia but had no influence on the above marrow changes. Cortisone was partially effective in restoring a normal myelogram.

In a comprehensive study of the relation of the adrenal gland to blood formation in the rat, Gordon and co-workers (61) found that adrenal cortical extract, cortisone, and epinephrine prevent the anemia following adrenalectomy in the rat, whereas Compound A and DCA[1] do not. They found the anemia following adrenalectomy to be characterized by a reticulocytosis and decreased red cell fragility and observed marrow changes similar to those described above. These authors conclude that the adrenal cortex plays a direct regulatory or supporting role in blood formation. Megel & Gordon (62) believe the altered red cell fragility noted above is due to a lysis inhibiting factor(s) in the plasma which is increased in the adrenalectomized rats since the increased resistance was not found when the red cells were washed.

De Bias (63) studied the effect of gonadal and thyroid hormones on the red cell count. He presents evidence that whereas testosterone increases the red count of ovariectomized rats, it has no influence on the count of ovariectomized-thyroidectomized animals.

Miscellaneous observations.—A fundamental advance has been made in our understanding of the pathogenesis of sickle cell disease. The observation by Pauling and co-workers (64) that S Hgb[1] is electrophoretically different from N Hgb[1] has led to a thorough reinvestigation of the changes which induce red cells to undergo sickling. Harris (65) has shown by the use of the phase microscope that deoxygenated S Hgb molecules align into parallel

aggregates which result in birefringent tactoids. A sickle cell is probably a membrane covered tactoid. Since S Hgb is less soluble in the reduced state than is N Hgb, the phenomenon of sickling results from the crystallization of the reduced S Hgb with the formation of hemoglobin aggregates, the latter causing the increased viscosity of the blood and increased mechanical fragility at reduced oxygen tensions. Sicklemia trait cells have less of the S Hgb than the cells from patients with sickle cell anemia which contain S Hgb in a concentration of from 80 to 95 per cent of the total hemoglobin [reviewed by Singer (66)].

Values for the life span of the normal red cell of various species have been well established, particularly by the use of radioactive isotopes. Recent studies indicate that these values do not necessarily hold true in various blood dyscrasias. Thus, the erythrocytes formed as a response to hemorrhage in the rabbit [Neuberger & Niven (67)] and in the rat [Berlin & Lotz (68)] have a shorter life span than those of normal animals, which indicates that when red cells are produced rapidly they are functionally poor. The mean red cell life span may also be shortened in some human blood dyscrasias. Berlin *et al.* (69) found this to be the case in patients with anemia and chronic leukemia and also to a lesser degree in polycythemia. Their study and that of Ross and co-workers (70), who found leukemic patients showed increased rates of destruction of transfused normal red cells, should stimulate a revision of our present concept of the mechanism of anemia in neoplastic disease.

The Leukocyte Series

Hormonal effects on eosinophils.—There have been a large number of studies on the influence of adrenocortical hormones on the number of circulating eosionophils. Since the discovery of the effect of these hormones on eosinophil numbers, several modifications of direct methods for counting these cells were developed. Although they are less laborious than differential counts on stained flood films, they are subject to numerous sources of error. The advantages, disadvantages, and problems encountered with the techniques now in use have been discussed most recently by Bonner (71) and Speirs (72). Speirs (73) has designed a modified hemocytometer which allows faster and more accurate direct eosinophil counting.

A quantitative relationship has been established between hormone dosage (ACTH, cortisone, and Compound F) and the degree of eosinopenia [Rosemberg & Lewis (74); Speirs & Meyer (75); Halberg & Visscher (76)]. Compound F and cortisone are apparently the most effective eosinopenic agents whereas Compound A, sex steroids, and DCA are relatively inactive (75). The latter compound and Compound A are effective in producing eosinopenia when massive doses are given to adrenalectomized animals [Speirs & Meyer (75); Scott (77)]. In spite of this quantitative relationship between amount of hormone administered and decrease of eosinophils, an eosinophilia of significant degree is not consistently maintained in adrenalecto-

mized animals [Speirs & Meyer (78); Brown (79)], hypophysectomized or splenectomized animals [Speirs & Meyer (78)] or in patients with adrenal insufficiency [Recant *et al.* (80); Prunty (81); Forsham *et al.* (82)].

The factors responsible for increasing eosinophil levels are not well known and experimental evidence is meager. Vaughn (83) has reviewed the relation of eosinophilia to over 52 diseases and concludes that increased histamine is the common factor in the production of eosinophilia. Histamine administration was followed by increased levels of eosinophils in guinea pigs [Vaughn (83); Halpern & Benos (84)]. Dury (85) noted an increase in eosinophils in adrenalectomized and splenectomized rats given epinephrine.

Numerous stress stimuli have been found to cause eosinopenia through activation of the pituitary-adrenal axis. Emotional tension (86), surgical operations (87, 88), coronary occlusion (89), electroshock (90), heat and cold (79), low oxygen tension (91), and epinephrine (92) are examples of such agents. The use of epinephrine-induced eosinopenia as a diagnostic test for Addison's disease has been questioned since epinephrine produces a decrease of these cells in a large number of Addisonians who do not respond to ACTH [Coste *et al.* (93); DeFossey & Deltour (94); Waldenström (95)] and even the response of normal subjects to epinephrine is inconstant [Broch & Haugen (96); Ferguson (97); Kark & Muehrcke (98)]. The eosinopenic response to insulin has been suggested as a more accurate test since the values are more constant providing blood sugar levels fall below 35 mg. per cent [Perlmutter & Mufson (99)].

The disappearance of blood eosinophils following increased hormonal output could be due to decreased production, sequestration in blood vessels of large organs, movement into tissue beds, or increased destruction. There does not appear to be a decrease in eosinophils in the bone marrow at the time of maximum eosinopenia [Rosenthal *et al.* (100)], although an increase in immature eosinophils was noted [Durgin & Meyer (101)]. This latter finding suggests an inhibition of maturation. The evidence for sequestration in the spleen is conflicting. Although Spain & Thalhimer (102) found that eosinophils accumulate in spleens of mice during the period of eosinopenia, the majority of investigators were unable to demonstrate eosinophil sequestration in rat spleens [(Best *et al.* (103); Solomon & Humphreys (104); and Fruhman & Gordon (105)]. Eosinopenia also has been found in splenectomized animals by Dury (85).

The suggestion has been made that eosinopenia may result in part from movement of eosinophils from the blood into the extravascular loose connective tissue [Dougherty (106)]. Pycnosis and fragmentation of blood eosinophils has been observed by Godlowski (31), Padawer & Gordon (107), and Poel & Becken (108). Padawer & Gordon (107) observed destruction and subsequent phagocytosis of eosinophils in peritoneal fluid of epinephrine-treated rats. Heparin appears to prevent the *in vitro* and *in vivo* eosinopenic effect of cortisone [Godlowski (31); Lewis & Kark (109)]. It appears to the reviewers that the strongest evidence thus far presented favors the concept

that adrenocortical hormones act on the eosinophils in a similar manner as on lymphocytes, i.e., by an eosinolytic action.

The value of the eosinopenic response as compared to the lymphopenic response as a clinical test for adrenal insufficiency has been expounded by Thorn *et al.* (110) and Roche and co-workers (88). Numerous investigators, however, have cautioned that such a test must be better standardized and that more than one determination must be made on each subject to draw valid conclusions [Best & Samter (111); Fisher & Fisher (112); Flink & Halberg (113)]. Roninger (114) found that in infants the lymphopenic response is more reliable following ACTH administration than is the eosinopenic response.

Hormonal effects on lymphocytes.—The earlier reports [reviewed by Dougherty & White (115)] that stimulation by the pituitary-adrenocortical axis produces a rapidly appearing lymphopenia ("lymphopenic response") have been confirmed and extended. An acute lymphopenia has been reported following administration of Compound F in normal humans [Fourman *et al.* (116)]. Adrenal cortical extracts and ACTH produce a lymphopenic response in normal individuals and infectious mononucleosis patients [Saunders & Adams (117)], but, in general, a lymphocyte decrease is less frequently noted in hormone treated patients with hematological dyscrasias, [reviewed by Wintrobe *et al.* (118)].

A sustained drop in lymphocytes has been reported following chronic administration of ACTH or cortisone to mice [Quittner *et al.* (119); Kass *et al.* (120)], and to rats [Asling *et al.* (121)] or following cortisone administration to adrenalectomized rats [Gordon *et al.* (61)]. Kumagai & Dougherty (122) have established the minimum effective dose of cortisone which produces a sustained lymphopenia in adrenalectomized mice, and also that amount which will maintain the blood lymphocytes within the range characteristic for intact animals. Tompkins (123) reported that adrenal cortical extracts produce a monocytopenia in rabbits which is comparable in time of initiation, duration, and degree to the lymphopenia in hormone treated animals.

The reports on various stress stimuli which produce an acute drop in circulating lymphocytes are too numerous to mention. The lymphocyte response to epinephrine has been most thoroughly studied in human and experimental animals and appears to be biphasic in character with a primary rise in lymphocyte levels (Phase I) followed by a decrease to lymphopenic levels (Phase II) and a subsequent return to normal [Michael (124); White *et al.* (125); Samuels (126)]. The adrenal medulla may participate in mediating Phase I of the response (124). The lymphopenic phase, however, is not dependent upon adrenal medullary discharge or epinephrine itself since lymphopenia occurs in animals with denervated adrenals and following ACTH in hypophysectomized animals [Colfer and co-workers (127)].

There has been confirmation of the lymphocytolytic action of C-11-oxysteroids by the use of *in vitro* methods. Schrek (128, 129) has demon-

strated a direct destruction of lymphocytes by adrenal cortical extract and cortisone but not by DCA. Feldman (130) reported a greater degree of *in vitro* destruction by lipoid soluble adrenal extract (Lipo-Adrenal Extract) than by aqueous adrenal extracts and even less damage with Compound A (dehydrocorticosterone). Similar results (unpublished) have been observed in the authors' laboratory. By his methods, Feldman (130) did not find any effect with Compound E, DCA, testosterone, growth hormone, ACTH, or insulin.

There have been several reports that the hypothalamus plays a role in regulation of numbers of blood lymphocytes [Colfer *et al.* (127); Simms *et al.* (131); Rosenow (132)]. Colfer and co-workers (127) suggest that the hypothalamic control is exerted by the influence of the hypothalamus on the pituitary-adrenal system. Weisberger and associates (133) found most transfused lymphocytes in the lung and suggest that the lung may have a homeostatic action in maintaining normal leuckoyte numbers.

It appears that the polymorphonuclear leukocytosis following administration of adrenocortical hormones is not dependent on or mediated by endogenous adrenal cortical secretion [Samuels (126); Palmer *et al.* (134); Stein *et al.* (135); Dury (136)].

Dougherty & Kumagai (137) have followed the blood picture of stressed adrenalectomized mice. They find there is an acute lymphocytosis following several types of stress which is the inverse image of the lymphopenic response in intact animals. This was called the "lymphocytotic response."

Alterations in lymphocyte morphology as well as lymphocyte numbers occur during the lymphocytotic response [Dougherty & Frank (138)]. These changes resembled the type II cells of infectious mononucleosis. This type of cell, however, is not pathognomonic of this disease since it is found in many viral as well as nonviral diseases [Litwens & Leibowitz (139)]. Dougherty & Frank believe this type of cell is a sensitive indicator of a relative adrenal insufficiency since the number of these cells diminish during ACTH or cortisone treatment.

"L. E. phenomenon."—Hargraves & co-workers (140) described a specific cellular abnormality, the "L. E. cell" in centrifuged heparinized bone marrow preparations from patients with acute disseminated lupus erythematosus. These cells were polymorphonuclear leukocytes which contained an amorphous inclusion body. It has been subsequently demonstrated that this phenomenon can be found in films of buffy coats of centriufged oxalated blood of patients with this disease [Sundberg & Lick (141)]; is not dependent upon use of anticoagulants [Eppes & Ludovic (142)]; and may be produced *in vitro* [Berman *et al.* (143)]. To demonstrate this phenomenon, a factor present in the plasma of a large percentage of patients in the acute phase of disseminated lupus erythematosus must come into contact for a certain period of time with a phagocytic type of cell. The plasma component was found to reside in the γ-globulin fraction of the patient's blood by Haserick & coworkers (144) and Berman *et al.* (143). The inclusion bodies are most com-

monly found in mature polymorphonuclear leukocytes although they have also been described in immature neutrophils, mature eosinophils, and monocytes [Moyer & Fisher (145)] and in basophils but not in monocytes [Rohn & Bond (146)]. Chemical studies revealed that the phagocytized material is nuclear in origin and consists of partially depolymerized desoxyribosenucleic acid [Lee *et al.* (147)]. Although the relation of the "L. E. phenomenon" to the pathogenesis of acute disseminated lupus erythematosus is not known, it has provided the only specific laboratory test for this disease.

Miscellaneous observations.—A lower leukocyte count with decreased absolute number of neutrophils and increased numbers of lymphocytes was found in the postwar German population when compared to prewar standards (148). Poorer nutrition and psychic factors were considered as causative influences. A similar shift in neutrophil/lymphocyte ratio was reported in populations living at high altitudes by Chiodi (149).

A leukocytosis described in vitamin E deficiency was attributed to an increased synthesis of creatinine, a substance believed to be important in white cell production [Dinning (150)]. Cysteine also seems to have an effect on leukocyte numbers since it has been shown to ameliorate the leukopenia seen after irradiation [Patt *et al.* (151); Rosenthal *et al.* (152)], and after nitrogen mustard treatment [Weisberger & Heinle (153)].

Determinations of the rate and site of destruction of leukocytes were made using new techniques. The life span of leukocytes was calculated by Kline & Cliffton (154) who incorporated P^{32} into the desoxyribosenucleic acid of human leukocytes and found the average life span to be 12.8 days. This high value as compared to reports of others was explained on the basis that most other methods calculate the rate of replacement of cells rather than total life span. These studies lend confirmation to the fact that the acute depletion of lymphocytes and eosinophils from the circulation after ACTH and cortisone is not due merely to inhibition of production of these cells. Van Dyke & Huff (155), using a method of exchange of cells in parabiotic rats, report the survival time of mononuclear cells of 38 min. and polymorphonuclears of 170 min.

The role of the lungs in the removal of leukocytes from the circulation has been studied by several groups of investigators [Weisberger *et al.* (156); Lanman *et al.* (157); Bierman *et al.* (158, 159)]. These studies provided additional evidence that the lungs are an important site of leukocyte disposition and that sequestration of cells in the lung may explain the leukopenia of anaphylaxis. A new technique of tracing transfused lymphocytes developed by Farr (160) may be of value in reaching the final solution of the problem of the site(s) of removal of circulating leukocytes.

The role of the spleen in the regulation of blood leukocyte numbers was investigated by Palmer & co-workers (161). These authors favor the theory that this organ acts by suppressing leukopoiesis or by release of leukocytes through a hormonal mechanism. Wright *et al.* (162), on the basis of leukocyte counts on splenic arterial and venous blood during epinephrine treatment, concluded that the spleen acts primarily by withholding cells.

Various blood and tissue factors have been described which increase [Steinberg & Marin (163); Oliver & Tramontana (164)] or decrease [Kemp *et al.* (165)] leukocyte numbers. The chemical composition of these agents and their relation to the substances influencing leukocytes in inflammation [Menkin (166)] awaits further study.

The Thrombocyte Series

Methods.—An analysis of the effect of various anticoagulants on platelet morphology has been made by Brecher & Cronkite (167). They found changes which occurred rapidly with all the solutions tested as well as with normal saline. These authors also described a technique for counting platelets which they claim is more accurate than those commonly used. The numbers of platelets of several individuals counted by this new technique at successive intervals remained constant. Scheff & Ralph (168) have also developed a more accurate counting method which, because it is laborious, is particularly applicable only to research problems. Hirsch *et al.* (169) investigated the viability and survival time *in vitro* and *in vivo* of platelets isolated and concentrated by various techniques.

Techniques of separation and transfusion of platelets have been improved. Satisfactory methods have been devised to obtain large yields of platelets for transfusion into thrombocytopenic individuals. Freeman (170) described a method by which platelets are collected in a resin container as a by-product of routine blood collection and can be separated in this manner without the damaging effects of centrifugation and washing. Dillard *et al.* (171) developed a simple method of platelet separation using sodium sequesterene as an anticoagulant with collection into silicone glass. Platelets collected by this method and transfused into thrombocytopenic dogs remained in the circulation 24 to 48 hr. reversing the coagulation defect and hemorrhagic tendency. Hirsch & Gardner (172) transfused platelets by the use of multiple silicone-coated syringes into humans with various thrombocytopenic conditions. They found these platelets persisted in the circulation from 5 to 6 days with the exception of thrombocytopenic purpuras.

Alterations of platelets in disease.—Kissmeyer-Nielsen (173, 174, 175) made a thorough reinvestigation of bone marrow and blood thrombopoiesis in various thrombocytopenic conditions, i.e., pernicious anemia, acute and chronic idiopathic thrombocytopenic purpura, and thrombocytopenia secondary to various splenomegalies. He concluded that the mechanism causing thrombocytopenia in all of these conditions is similar, i.e., the decreased number of blood platelets is due not to a decreased number or "shift to the left" of megakaryocytes in the marrow, but to abnormal megakaryocyte function manifested as diminished platelet production. The basic cause remains unexplained although the above author favors alteration in function of the spleen or perhaps the entire reticuloendothelial system.

Significant advances have been made in our understanding of the platelet defect in idiopathic thrombocytopenic purpura. Harrington and co-workers (176) demonstrated a thrombocytopenic factor in the blood of patients with

this disease which was located in the globulin fraction and which did not always disappear after splenectomy. A similar factor was found in normal human blood, plasma, or serum which, however, did not cause as marked an alteration in platelet levels [Stefanini & Chatterjea (177)]. The nature of this substance is not known nor is the role it plays in the low platelet numbers seen in thrombocytopenic purpura. A nonspecific platelet reducing factor was also found in spleens of patients with thrombocytopenic disease [Platt & Zeller (178)].

Much evidence has been accumulated that transfused platelets have a shorter survival time in thrombocytopenic purpuras, lasting 0 to 3 hr. in the primary disease and 12 to 96 hr. in secondary cases of thrombocytopenia [Hirsch & Gardner (172); Stefanini *et al.* (179, 180)]. In a search for a mechanism to explain low platelet levels in the primary disease, Stefanini and coworkers (181) were unable to demonstrate any evidence for selective sequestration of platelets by the spleen, and more recently Stefanini, Chatterjea & Dameshek (182) reported negative evidence on platelet removal by the pulmonary circulation.

Thus, a humoral factor has been demonstrated in the primary form of thrombocytopenic purpura, but whether it is endocrine [Lozner (183)] or antibody [Ackroyd (184); Evans *et al.* (185)] in nature is still debated. There are several reports that cortisone and ACTH raise platelet levels of patients with this disease, but the mechanism of action of these hormones is not known [reviewed by Stefanini *et al.* (186)].

Reports on the effect of adrenocortical substances on platelet levels in nonthrombocytopenic animals and humans are conflicting. Greer & Brown (187) were unable to find any effect of pituitary ACTH preparations on platelet levels in humans or rats. Similar results were reported by Adams (188), for ACE[1] treatment of rats. Adams noted a significant decrease of platelet levels in hypophysectomized rats which he explained on the basis of the altered metabolism following hypophysectomy. Lauridsen *et al.* (189) more recently reported a precipitous drop in platelets within 1 hr., becoming maximum at 2 to 4 hr. following injection of 50 or 100 mg. ACTH into normal humans and into one splenectomized individual. It is possible that the earlier negative reports were due to the use of weaker preparations, inadequate dosages, and observations at different time intervals.

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PERIPHERAL CIRCULATION[1,2]

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The time devoted to the preparation of this review has been grossly inadequate to cover even the papers published from August 1951 to August 1952. Apologies are tendered to the authors of outstanding papers whose work is not even mentioned.

No one seems able to define "peripheral circulation." Does it include the circulation of the viscera, the brain, the lungs? Some even have replied that it included everything outside the heart itself and were not sure that even the coronary circulation should not be included. After all, the term "peripheral" must mean something in the phrase. The author therefore feels justified in giving his own definition, which is that for the purposes of this article "peripheral circulation" includes those topics which are here discussed and excludes those that are not. In general, the great numbers of papers which have as their main interest the cardiac function itself are omitted, though where the cardiac output is the chief interest they may be mentioned, since cardiac output measures the total peripheral circulation. Papers on electrocardiography have been omitted with a sigh of relief. (It is worth pointing out here, however, that at long last several workers in the field have realized that if their apparatus measures voltage correctly, the algebraic sum of three voltage differences in any electric field must, taken in cyclic succession to return to the same point, automatically add to zero. Far too many papers have been written under the delusion that this fundamental law of physics, if it were obeyed in electrocardiography, had some bearing on the validity of the hypothesis of Einthoven's equilateral triangle. If the measured voltage differences at any instant do not sum to zero, this reflects not upon Einthoven but upon the design of the recording apparatus.)

In the fields of research on the circulation concerned with vasoactive substances in hypertension and in shock, and to some extent in cardiac dynamics, a reviewer is forced towards the position of Descartes (1),

> when I considered the number of conflicting opinions touching a single matter that may be upheld by learned men, while there can be but one true, I reckoned as false all that was only probable.

It is surely no coincidence that the fields of confusion and controversy are those where the methods of measurement in favour are often those which

[1] The survey of the literature pertaining to this review was concluded in July, 1952.

[2] The following abbreviations are used in this chapter: BCG (ballistocardiograph); EKG (electrocardiogram); ACTH (corticotropin); DCA (desoxycorticosterone acetate); VEM (vasoexciter material); and VDM (vasodepressor material).

lack any quantitative validation, where the parameter measured is loosely defined and often assumed to be something else than it is, and where little attention is paid to statistical evaluation of results (though this is most appropriate where so many uncontrollable variables are involved).

Apparatus and Methods for Study of the Circulation

Haemodynamics must be the oldest of the branches of physiology, according to a most interesting article on the ancient art of feeling the pulse (2). Books were in existence in China on the subject in 2500 B.C.

Every year old methods are improved and new apparatus and methods are added. A "quantitative stethoscope," which in its simplicity shows the touch of genius, has been described (3). A variable orifice at the throat of the bell is adjusted by the twist of a dial, until a given murmur is no longer heard, when the decibels attenuation can be read off the dial. Another device commendable for its simplicity for clinical use is an apparatus for measuring venous pressure (4). The needle inserted into a vein is connected through a plastic tube, where the fluid-air meniscus of fluid is observable, to a closed metal bellows. One turn of a screw compressing the bellows raises the pressure from 0 to 60 cm. H_2O, so the pressure required to stabilize the meniscus against the venous pressure is easily reached. Developments in the rabbit-ear-window technique, so that ultraviolet microscopy is possible, have been described (5).

For the investigation of "tone" in isolated perfused segments of blood vessels, these are placed inside a closed chamber, the pressure of which is read by an "isometric" manometer (strain gauge). With epinephrine, using the mesenteric artery of a dog, pressure rises up to 100 mm. Hg are recorded (6). The sensitivity would appear to depend upon having a lack of distensibility in the rest of the closed perfusion apparatus. Others are using strain gauges in a similar manner (7).

In Europe, particularly with the French physiologists, a different technique of following vasomotor changes is popular. The organ or tissue of interest is perfused, not under constant pressure, but by a positive action pump at a constant flow (method of Jouvelet) (e.g., 8, 9). The changes in tone of the vessels are indicated by the changes in perfusion pressure. There have been several modifications in such pumps. An excellent discussion of the available types of "artificial heart pump" is given by Dubbelman (10), including modified Dale-Schuster types and tubal pumps. He finally used the periodic pressure valve that is commercially available for operating milking machines, in an ingenious application. A tubal heart pump designed for the purposes of heart surgery (11) and two pumps by which the arterial pulse curve in the aorta can be imitated have been described (12, 13). These are intended for an interesting reversal of the classical method of the heart-lung preparation (in which the heart was isolated and an artificial peripheral circulation provided), for the plan here is to retain the physiological peripheral circulation and substitute a pump for the heart. Results should enable us to

disentangle peripheral effects of drugs from the complications resulting from their cardiac effects. Evidence has now been produced indicating that, in the modification of the heart-lung preparation in which the lungs are perfused directly from a venous reservoir, there is a vasoconstriction of the lung vessels which is eliminated by coronary venous blood (14). A new scheme for studying tone in heart muscle is to tie off all outlets of the ventricles of an isolated heart and record the pressures within when the volume is kept constant during a cardiac cycle. The coronary circulation is supplied from a donor dog (15). The method is far from physiological but should give interesting results as to the differences between isometric and the normal contraction and relaxation of the heart.

More and more catheterization of the cardiac and pulmonary vessels in animals and humans is being used. A balanced judgment of an authority as to the usefulness in study of congenital cardiovascular anomalies has been written (16). The methods are not without their serious dangers (17, 18, 19). The authors of the last give us the doubtful reassurance that "if the induced arrhythmias are not fatal, they may usually be expected to disappear within twelve hours."

For recording pressures electromanometers are most popular, though some of them are annoyingly insensitive. A circuit for amplification of the output of strain gauges (20) is described, but since it ends in a slow-response Esterline-Angus recorder, there seems little point in using a transducer at all instead of direct liquid manometers. It is not sufficiently realized by physiologists (and not often admitted by radiophysicists) that the only justification for the use of electronics is the unlimited speed of response available. Where this is not a requirement, physiologists are much better off with glass tubes of saline or mercury. The mechanoelectronic transducer which developed from the "Claustron," i.e., RCA-5734, will be increasingly a boon to physiologists, and should eventually displace condenser manometers and strain gauges. Again it has been used (21) for recording peripheral pulse contours, but with a mirror galvanometer at the end of the circuit, so the advantage of speed of response is thrown away. In such an application, the classical optical recording from rubber membranes would be preferable, except perhaps for the convenience of wires instead of tubes.

For measurement of peripheral flow, a tool that is being used more is the clearance of radioactive Na^{24} or I^{131} from tissues (Kety's method) (22 to 25). Most of the authors are wise in that they do not use the term "flow" instead of "clearance" in their titles and realize that other factors than flow, such as a change in permeability of the blood-tissue barrier, can be involved. There have been some evidences of lack of correspondence with blood flow in muscle (26, 27) but this might be due to inaccuracies in measurement. The curve of disappearance, with muscle injections, may be a combination of that of muscle and of skin due to leakage into skin when withdrawing needle). Where the semilogarithmic plot is not linear, it is claimed that the two underlying clearances, for skin and muscle, can be obtained from the initial and final

slopes on the graph (22). However, the sample graph given does not convince one that the separation into two straight lines is justified. I^{131} has also been used to measure circulation time (28).

A long overdue analysis of what is meant by "circulation time" has been made (29). The end point of a measurement is not the arrival of the first trace of the injected substance, nor the reaching of any average concentration, but a "detectable" amount. Thus, the injection of a diminished concentration, or the same dose injected into a larger volume which will dilute it, will give a longer circulation time. Experimentally, with dehydrocholic acid (Decholin) and the bitter taste as the end point, injection of a 30 per cent solution gave a circulation time 15 per cent shorter than with injection of a 10 per cent solution. With patients in heart failure (dilated hearts) the circulation time was much longer, and probably the "pooling effect" of a larger volume of heart and lungs is responsible, rather than reduced output. Fluorescein injected into the right ventricle by catheter has been used to give the circulation time to the face, its arrival being observed in the oral mucous membranes under ultraviolet light. If the time is less than 4 sec., a congenital shunt is indicated (30). The trouble has been, not so much how to measure circulation time, but what to do with it when you have it.

The electromagnetic flowmeter, which a few years ago appeared rather bulky and liable to errors in voltages from electrodes on the outside of the artery, has now been developed into a useful tool (31). However, the feature that the continuity of the artery was not broken is now lost. Electromagnetic recording has been added to the rotameter (32), and photoelectric signalling to the bubble flowmeter (33). For the study of the velocity curve rather than total flow, a pitot head has been inserted through a slit in the pulmonary artery (34). While this may give a good method for studying changes in velocity and investigation of vasomotor effects, it is doubtful if it can tell us much about the undisturbed velocity pulse in vessels, since the form of this pulse depends greatly on their distensibility, which must be modified by the apparatus. The "Potter turbinometer," which is said to follow pulsating flow accurately, has been similarly inserted in the aorta to measure cardiac output (35). (It is most annoying in this and some other papers that no reference to the instrument is given except to a paper "in preparation.")

The number of workers using the BCG[2] to measure "cardiac output" seems to be increasing. The portable type in which the subject lies on a rigid table and the apparatus rests on the thighs (36, 37) has been shown to give the same results as the other type (Starr) with suspended table (38). Some workers add an attenuated EKG[2] to the BCG record to help identify the complexes (39, 40). However, an important study (41) has been made from the literature of the relation of "cardiac output" measurement by the high frequency BCG, the low frequency BCG, ethyl iodide, acetylene, and direct Fick methods in relation to body surface area. The estimates of cardiac output from the high frequency BCG turn out to be unrelated to the body size of the subject. The low frequency BCG and the other methods give results which

correlate with the surface area. This peculiarity to the high frequency BCG is not due to random errors in the machine, but simply indicates that it is not measuring cardiac output at all, but something else—the force or "impulse" of cardiac ejection. The realization of this should enhance, not decrease, the value of the instrument, for there are many methods for cardiac output but no other for cardiac impulse. In 195 cases of coronary disease, 23 per cent who had normal steptest EKG's showed abnormal BCG's (42) (judging from the form of the waves, without calculating "cardiac output"), and abnormal patterns of BCG waves are seen in cardiac failure (43). (The calculated "cardiac output" in this paper does not seem very creditable, 8.2 l. per sq. m. per min. after digitalis in one case.) Similarly changes in BCG wave pattern, rather than calculated cardiac outputs, are seen after smoking (44), which it is stated (without very convincing evidence) are much greater than could be due to the incidental deep breathing. Increases of up to 50 per cent in "cardiac output" by BCG are reported in patients after operation (45). The true cardiac output may not have changed at all in this case, only the impulse of the heart. The BCG has been judged valuable in heart disease, angina pectoris, and myocardial infection (46) because of the changes in the wave forms. These abnormal waves may either increase or decrease the supposed estimate of cardiac output (47). They are supposed to be due to asynchronous ejection by the two ventricles. In view of the fact that the BCG does not measure cardiac output (but something else probably quite as valuable), it would seem quite inadmissible to subtract from ballisto "cardiac outputs" the output of the left heart calculated from the aortic pressure pulse to arrive at the output of the right heart. This has been done (48), in an attempt to analyse the respiratory changes. Again it is not sound to calculate peripheral resistances from ballisto "outputs."

An older method of calculating cardiac output (Bazett's and Remington and Hamilton's method) from the arterial pulse wave contour has been tested against simultaneous rotameter measurements of aortic flow in dogs (49). The average difference was ± 13 per cent, with a range of $+37$ per cent to -40 per cent. All stroke volumes calculated from pulse contours fall from 14 to 40 per cent below rotameter measurements when the diastolic pressure was above 120 mm. It is not clear in this paper whether or not corrections for the raised diastolic pressure level were applied to the pulse wave velocity, which enters the equations. It should seem that this method can be relied upon only where pulse-wave velocity is actually measured. Similar principles of analysis of the pulse contour have been applied to the volume pulse of the finger tip (50), but our own experience would indicate that the distensibility factor varies so much with slight changes of venous distension that even the shape of the pulse curves is difficult to interpret. The third derivative of the finger pulse curve resembles the BCG (if anyone can make anything out of that!).

Cardiac output has also been measured by the dilution of a dye injected into the right ventricle, and by sampling the concentration in the pulmonary

artery. A good analysis of this method has been made (51). It can yield the circulation time, the cardiac output, and the size and location of the volumes of blood with which the dye is mixed. The same method, using I^{131} labelled serum albumen and a counter instead of a dye, has been compared with simultaneous rotameter measurements (52). The output by the dilution method averaged 15 per cent higher than with the rotameter. The error was consistent. Part of this must be due to the fact that the rotameter output does not include the coronary circulation. Essentially the same method has been used, with dye, to determine the residual volume of blood in the right ventricle of normal and diseased human hearts *in vivo* (53). It was established with a mechanical model that the slope of the dye dilution curve was linearly related to the ratio of residual volume to stroke volume. In normals, the residual volume was 89 ml., with a stroke volume of 54 ml. and the ratio of residual volume to stroke volume ranged from 0.5 to 3.7, with a mean of 1.75. In dilated hearts (of hypertensives in failure) the residual value was from 192 to 542 ml. and the ratio averaged 13.6. Perhaps this paper will at last dispel the fog of the fallacy, believed by many physiologists, that the normal heart "empties" itself almost completely, and that "efficiency" of the heart demands this. On the contrary, the heart is a very important reservoir of the circulation. An attempt has been made to use the oximeter with arterial blood passing through a cuvette or on the ear to give the dilution curve. Compared to the direct Fick method, the differences in cardiac output ranged from -26 to $+23$ per cent, and the authors conclude this is not good enough.

Measurement of blood volume can be made by the use of red cells labelled with radiophosphorus (54). There is no loss of radiophosphorus up to 5 hr. In dogs put into haemorrhagic shock, there is a delay in mixing time and a steady decline in concentration after mixing, not seen before shock. This is thought to be due to slow dilution of the "circulating blood" with unlabelled cells from stagnant "back-waters." The radiophosphorus technique has been ingeniously adopted to measure the blood volume in various viscera in dogs (55). The area of interest is tied off before the labelled cells are injected. When the ligature is then released, there is a drop in activity of blood samples as the unlabelled blood dilutes that which was circulating. The volume in intestines, liver, spleen, and stomach vessels has been measured. K^{42} can also be used to label red cells for blood volume measurements (56).

Another method for measuring flow devised in recent years is that used for brain circulation (Kety & Schmidt's method) employing nitrous oxide, and also used by some for coronary flow. Its use on "elderly" patients (over 50!) with hypertension emphasizes an intrinsic disadvantage of the method (57). This is that it measures the flow per 100 cc. of "active tissue," and if large areas of tissue are without blood flow (e.g., infarcts) and also metabolically inactive, the flow would appear normal. A lack of correlation was found between the cerebral symptoms and the measured flow.

X-ray densitometry is also a means of investigating the circulation. The portal circulation is now investigated in man by injection of contrast

material through the skin and liver (58, 59). The "electrokymograph" gives some quantitative measures of x-ray densities (60).

Oddments are the "tonoscilloscope" (61), an automatic ink-writing oscillometer connected to an inflated cuff on the limb, which is found to be no good for measuring blood pressure, and the "angioplethysmokymograph" (62). This is for measuring the volume changes of isolated vessels when drugs are applied. Bost (63) describes a simple plethysmograph for pedicular organs, which confines the tissue between a rigid diaphragm and a rubber membrane. Investigation of the blood flow of the intestines in man has been made by the use of heated thermocouples, which are thermostromuhrs of the Gibbs type (64). The difficulties of ensuring adequate and constant contact with the tissue in question is a serious one, and also care must be taken not to heat the tissue enough to cause vascular reaction. In general, the visceral blood flow was found to change in the opposite direction to that of the skin or limbs.

It would be natural to suppose that the most certain way of knowing the reaction of blood vessels to a given procedure was to watch them through a microscope. This is the basis of the measurement of reactivity of vessels of the rat mesoappendix to topically applied epinephrine (e.g., 65), and the change in that reactivity when pressor or depressor substances are injected into the tail vein. This test has been almost the only basis on which a great deal of theory concerned with the role of VEM^2 and VDM^2 material in shock has been built. The method has now been critically examined using accepted procedures and criteria (66). It is found to be quite unreliable as the responsiveness fluctuates greatly, the time and concentration of the agent presented is uncontrolled, and for other reasons. A basic difficulty, in our experience of watching living vessels (mainly in an experiment in the student laboratory) is that the eye is impressed chiefly by the speed with which the blood cells pass by in the field of view. This velocity of flow cannot be taken as an index of volume of flow, since a narrowing of a given vessel will increase the velocity at that place if the volume flow were to remain constant, while a decrease in volume flow with a given vessel of fixed calibre would, of course, reduce the velocity. If then the vessel under observation constricts more than the rest of the vessels in series with it, we may have a speeding up of the observed velocity, while the flow is reduced. This often will be interpreted as a general vasodilation instead of a vasoconstriction. We find students unable to determine whether the topical application of epinephrine is vasoconstrictor or vasodilator. There would be much more general confidence in the results of these workers if they would also use one of the many measurements of flow or of peripheral resistance now applicable to small animals (e.g., 67).

Measurement of Arterial Pressure

There has been what some of us consider a major setback to medical science in the publication of the recommendations for human arterial

pressure determinations by sphygmomanometers, the work of a committee of the American Heart Association (68, 69). For therein the committee advocates that the change (muffling) in the sound be not taken as the diastolic criterion or recorded as such, "except when necessary" and that the disappearance of the sound be adopted instead. This is an abandonment of physiological principle for an illusionary practical gain. For nothing could be more certain than that stream-line flow of the blood stream is silent, and that if it is heard, this is due to turbulence (70). The disappearance of the sound indicates the disappearance of the turbulence which was created by the high velocity of the stream issuing from the arteries narrowed by the cuff (whether the sound is due to the vibrations of the vessel walls or from eddies in the stream is irrelevant). There is no good reason why this disappearance of turbulence should coincide with diastolic pressure, which is the maximum pressure that will allow the artery to stay open throughout the whole cycle, when at no time in the cycle is the artery under the cuff completely closed. In practice with normal subjects at rest, it happens that soon after the decreasing cuff pressure has allowed the vessel to remain open all the time (i.e., after the true diastolic pressure has been reached) the degree of narrowing of the vessel that persists becomes insufficient to cause turbulence and sound. But this is incidental, as is very easily shown, if, as the author demonstrates to first year medical students, the two criteria are measured on any normal subject after exercise. The sound will then persist down to very low values, while the change of sound occurs at reasonable levels. Again while both criteria suffer from the errors of the inability of the cuff to transmit the pressure [which are much greater than generally realized (71)] so that from this both give too high a diastolic pressure, the judgment of when a sound has "disappeared" depends on the acuity of hearing, and the proper placing of the stethoscope bell. In contrast, there is a very good reason why the change in the sound should occur at diastolic pressure, for here the silent period at the end of diastole, when the artery is momentarily closed, has been eliminated and the sound is continuous, no longer "staccato." The committee states that "accuracy, not applicability to every individual, should determine the choice of criteria." This suggests an unorthodox view both of "accuracy" and of the scope of medical practice. (It is as if the psychologists were to tell us that, because on this continent personal income in general is related to intelligence, they now advocate the measurement of intelligence in terms of dollars.) Surely the practice of medicine is concerned with those who are not in the range of the norm (where coincidence makes the disappearance of the sound agree with diastolic pressure), but with those who are not normal.

As to evidence from direct comparison of arterial pressures measured by optical or electromanometers with those by the Riva Rocci cuff, these would have validity only when the two were made simultaneously on the same artery, and this has seldom been done in the references cited in the article. The convenience and the ability of electromanometers with small

catheters to follow correctly rapid changes in pressure, if their frequency characteristics are adequate, has led many to ignore the existence of the physiological "reactive errors" so important in our science. The instrument may measure correctly the pressure of the moment at the end of its catheter, but is that pressure the same as existed before the measurement in the undisturbed circulation? There is good evidence that it can sometimes be very different (72). Even where local anaesthetic is used in arterial catheterization, the artery may react by partial spasm near and at some distance from the catheter tip, and the presence of the catheter must affect the form of the pulse wave to an unknown extent.

The danger of this recommendation is that the teachers in our medical schools may pay attention to it, and we will be turning out doctors who do not understand what they are measuring in one of the very few applications of science to ordinary medical practice. A number of healthy young persons, unlucky enough to have persistence of turbulence in their arteries, longer than most, will be told by general practitioners that they should consider themselves cardiac invalids because of valvular incompetence.

The effect of the posture of the arm of the patient on the arterial pressure measurement has been tested (73) by comparing values with the arm down and the arm horizontal. With the latter, both in normals and in mild and severe hypertention, the systolic and diastolic pressures were 8 to 10 mm. lower. With the arm horizontal, no difference was found whether the patients were lying, sitting, or standing.

With regard to direct measurement of arterial pressures by electromanometers through catheters, an extension and modification of the theory of Hansen has been made (74). The theory did not take proper account of the effect of viscosity in damping the system. New equations are given and modified conditions are derived for the ideal "critical damping," which are not greatly different from Hansen's. A mathematical analysis of the inertia of pneumatic pressure transmissions has been made (75) in terms of the "half-time" of response. This is the time taken for the recorder to reach 50 per cent of its deflection when a sudden pressure change is made in the primary system.

Haemodynamic Quantities and Calculations; Pressure-Flow Relations

We are heading for confusion unless some agreement is soon reached on the proper use of "resistance to flow." Classically, by analogy with resistance to flow of electricity or thermal resistance, this should be simply the ratio of the difference of pressure across any portion of a vascular bed to the flow that results; i.e., it is a convenient factor by which the pressure drop is multiplied to obtain the flow. By its use, nothing is implied about the shape of the pressure-flow curve, any more than the accuracy of Ohm's law is implied when electrical resistance is used. The resistance so defined can tell us about the two factors on which it depends, namely the viscosity of the

fluid flowing and the geometry of the vascular bed (by Poiseuille's or other laws). It turns out that in vascular beds the relation between pressure and flow is not usually simple. Instead of a straight line it is curved one way or another and often is sigmoid, and flow becomes zero while there is still a positive pressure drop. This last fact is variously interpreted as the result of "critical closure" of vessels (76), due to a fundamental "instability" under the law of Laplace [which has wide application to the circulation (77)], of the existence of a "yield pressure" in blood, which is supposed to have "plastic flow." The last explanation is without basis, for the rheologists have found no trace of "plastic flow" nor "yield pressure" with blood, and the phenomena of zero flow at positive pressures are seen equally with pure liquids, like Ringer's solution, flowing in vascular beds. Because of this zero-flow-pressure, which is regularly seen in the perfused kidney (78), many authors are calculating the resistance to flow as the ratio of the difference between arterial pressure and this zero flow pressure (i.e., giving the supposed "working pressure") and the flow.

There are two reasons why this change in the calculation of "resistance" should be abandoned. First, it is based on a fundamental error in logic. Whatever the factor which causes the cessation of flow under positive pressure, it is quite certain that this factor does not exist when the flow is proceeding and the vessels open. It is a "potential" factor that operates only when the pressure is low enough. The driving force for the flow therefore cannot possibly involve this zero-flow-pressure. Secondly, to use this new calculation is to throw away the utility of "resistance" as an index of the geometry of the vascular bed. Often the fall of flow to zero is precipitous as the pressure is reduced, i.e., a very small change of pressure produces a big change in flow. Thus the "resistance" by the perverted calculations would be very low, much lower than if a higher pressure were used. Yet it is quite certain that the bore of the vessels is less, not greater, at the lower pressures. The classical "resistance," on the contrary, will increase (and become infinite when the flow is zero) as the pressure is lowered, indicating that the vessel size is decreasing.

In electronics, the analogous "instantaneous slope" of the characteristic curve is used, but always distinguished from the true resistance or conductance. We must be equally careful not to confuse the terms in haemodynamics. Another dangerous use of precise terms is the growing habit of some workers on cardiopulmonary dynamics of writing papers about "pulmonary capillary pressure." It is true that at present most of them still use quotation marks, but next year they may drop them (e.g., 79, 80, 81). This "capillary pressure" is that recorded from a catheter pushed up the pulmonary artery until it can go no further because it is jammed into a small vessel. Exactly what kind of vessel no one can tell. It will obviously register the pressure of the point where that vessel happens to connect with one in which flow is still free. This is assumed to be "capillary pressure" though often it is used in the subsequent calculations as the pulmonary venous pressure, or even

left atrial pressure. Apart from the uncertainty as to what are the interconnections of the impacted vessel to the free flow beyond, it would be measuring a pressure which might, by the operation of Bernouilli's principle, be actually lower than the venous pressure. Our own school of believers in critical closing pressure would suggest that the blocked off vessel would close and eject its contents retrogradely (this is probably why arterialized blood can be withdrawn) and that the critical closing pressure of lung arterioles is being recorded. Pressure-flow curves on the isolated lung (82) show what we could call a critical closing pressure of 15 cm. of water when the lungs are inflated, much less when deflated. There have been papers published in the year expressing criticism of the assumption of ability to measure "pulmonary capillary pressure." For example, the technique was used in five patients with septal defects where small vessels could be impacted from either end (83). The shape of the pulsation in "capillary pressure" resembled that of the artery, the mean pressure was higher than in both atria, and there was a considerable time lag between a rise in the systolic pressure and in an obstructed pulmonary vein. The pressure from a blocked artery was affected by the pressure of the venules and of a blocked vein by the arterial pressure. It is pointed out that an error of only 1 mm. Hg in the "capillary pressure" would result in an error from 15 per cent to 25 per cent in the calculations now commonly made. Another author (84), from experiments in which the left atrial pressure was measured as well as that from an impacted catheter, concludes that no confidence can be placed in the measurement of "capillary pressure" if there are seen any phase changes in pressure. These can be due to leak around the tip of the catheter and in such cases the pressure may greatly exceed the left atrial pressure. Why not drop the pretence, and call this pressure the "impacted small artery pressure"? No doubt it will be useful as long as we know what it is, or rather, what it is not.

In the case of pulmonary and cardiac haemodynamics, the fascination of working out equations, which are so impressive to the laymen, has seemingly overcome all scruples of common sense. As an example, in one paper "pulmonary arteriolar resistance," R_A, is calculated by the formula

$$R_A = \frac{(PA_m - \text{“}PC_m\text{”}) \times 1.332 \times 60}{CO}$$

where PA_m is the mean pressure in the pulmonary artery (measured by a catheter pushed there), "PC_m" is the mean pulmonary "capillary" pressure, and CO is the cardiac output. This might pass as long as we accept the interpretation of the pulmonary "capillary" pressure as that measured by a catheter jammed into a small vessel (any one will do) until it is plugged. The next equation however is for the "total pulmonary resistance" R_T

$$R_T = \frac{PA_m \times 1.332 \times 60}{CO}.$$

Hidden here must be the assumption that the pressure at the end of the pulmonary circuit, i.e., the end diastolic pressure of the left ventricle is zero or negligible compared to PA_m (though this is not explained in this particular paper).

"The difference between these two values was taken as the resistance provided by the stenotic mitral valve." Let us subtract the equations (which the authors do not do explicitly). We have for this resistance

$$R_{MV} = \frac{\text{"}PC_m\text{"} \times 1.332 \times 60}{CO}.$$

Then the values for the resistance of the mitral valve are based entirely upon the one measurement of pulmonary "capillary" pressure, together with the cardiac output, and that one measurement is of doubtful interpretation. As for the assumption that the end diastolic pressure of the left ventricle is always zero, in normals and these patients alike, no attempt is made to establish this. When this unreliable value of the resistance of the valve is then used with further impressive mathematics based on a hydraulic equation (85), which does not even approximately apply to the case, to calculate the area of the orifice of the mitral valve, the pinnacle of uncertainty is achieved.

The measurement of the elevation of pulmonary pressures in mitral stenosis is a valuable one and will serve as an index of the severity of the narrowing of the valve. Why spoil such a scientific measurement by building upon it such a house of cards, the deceptive facade of which may well mislead the trusting clinician into buying it? No attack upon the particular authors of the paper cited is intended, for they merely followed what has become a fashion mainly instituted by others.

A further step in using data from catheterization in haemodynamic calculations has been taken, all based on measurement of pulmonary arterial pressure and its pulsation (86). Not only the total pulmonary resistance (assuming the left atrial pressure is zero) is calculated, but the "elasticity resistance" of the lung vessels. The latter is deduced from the pulse pressure and the flow (cardiac output). This is an interesting reversal of the well-known method of calculating output from the pulse curve and the distensibility. A mild protest should be registered to the term "elasticity resistance," which is apparently the reciprocal of distensibility, and therefore is proportional to "elasticity" in the precise sense in which the physicist uses the term. (It is in no sense a resistance to flow.) This is compared to the resistance to flow, for the pulmonary and systemic circuits. The ratio of "elasticity resistance" to flow resistance is 3.5 for the pulmonary circuit and 1.2 of the systemic. It is difficult to interpret such a ratio which would apparently have the dimensions of the reciprocal of time. In congenital heart disease, the authors find that the adjustments in the systemic system are towards normal pressures, while in the pulmonary circuit the circulation suffers large changes from normal.

A very clearly presented and scientifically meticulous analysis has been made by Gomez (87) of the possibilities of calculating many parameters of the renal circulation from present measurements. The data required are the mean arterial blood pressure, the renal blood flow, and plasma flow, glomerular filtration rate, the protein concentration of the blood, and the renal venous pressure. From there can be calculated the total renal resistance R, the afferent renal resistance R_A, the "pure efferent resistance" R_E, and the "net efferent resistance R_E," and the venular resistance R_V. The assumptions are carefully stated and analyzed as to their validity. From data on 22 normal subjects and 51 with essential hypertension, the surprising conclusion is reached that in normals the renal venular resistance on the average equals the resistance of either afferent or efferent arterioles. In hypertension, the dominant change is an increase in afferent arteriolar resistance, which is greater than the increase in resistance of the systemic arterioles. This is a quite remarkable piece of work.

While the blood flow of the kidney is properly left to another reviewer, one or two haemodynamic developments need comment here, since they are concerned with pressure-flow relations. The astonishing report by Hooker and later by Gesell that renal function depended upon the pulse pressure as well as upon the mean pressure of perfusion has finally been disproved. Two independent workers find no change in renal clearances when perfused with a pulsating or a steady pressure of the same mean value (88, 89). More investigations of the changes in flow when the mean pressure is lowered (78, 90) verify that at high perfusion pressures (80 to 200 mm.) the flow is remarkably independent of pressure, but falls abruptly at lower pressures, to a final zero flow at a "yield pressure" (critical closure?) which may be as low as 10 mm. Hg. It has been suggested that the apparent "yield pressure" is really connected with the "intrarenal pressure" (91). This is obtained by thrusting a 20 gauge needle into the renal parenchyma, and connecting it to a nearly "isometric" manometer. Each millimeter fall or rise of arterial blood pressure causes a rise of 0.2 mm. in this measurement. It is difficult to see what this needle is measuring, and it would appear that it must be influenced by the cut vessels of all kinds which will communicate with the end of the needle.

As to the existence of a double vascular system in the kidney, the remnants of the group who discovered the "Oxford shunt" continue to publish convincing pictures of cortical ischemia while the medullary glomeruli are still perfused (92, 93). However, they now emphasize that they consider both cortical and medullary circulations as glomerular, so that they would not expect an alteration in clearance. This rather takes the wind out of the sails of opponents of the "kidney shunt," who continue to find no evidence of such in renal function (94), and the question becomes mainly one of haemodynamic interest. It is admitted (95) that the peripheral cortical glomeruli have a "lower threshold" (higher critical closing pressure?) than those that are deeper, but it is emphasized that this is not a "shunt." The

question has been investigated by the use of a Gibb's heated thermocouple thrust into the tissue of cortex and medulla (95). The flow was changed by nervous stimulation and vasoactive drugs. In all cases, the two regions seemed to have the same response. While it is mainly concerned with tubular damage, a paper on the pathology of acute renal failure after ischemia (96) contains some fine histological pictures showing focal cortical ischemia. Other evidence comes from studies of renal function in man after controlled hypotension (97).

After years of worrying about keeping up the arterial pressures during operation, surgeons are now deliberately lowering it by using blocking agents, or, most ingeniously, by using negative pressure on the legs to trap blood there (98, 99, 100). It would be interesting to measure the effects on kidney circulation and function.

Whether the parallel circulation of cortex and medulla of the kidney be considered as a "shunt" or not, the sigmoid shape of the pressure-flow curve would be a consequence of two parallel circuits having different tendencies to critical closure. The independence of flow and pressure at high pressures, however, seemingly would not be explained on this basis and would require the postulation of some specific reflex mechanism of control, for it implies that the blood vessels are smaller as the pressure is raised.

A new suggestion that the glomerulus represents "a coupled elastic ram," capable of elevating the pressure of the filtrate to as much as ten times that of the efferent arteriolar pressure by momentum transfer (101) requires study. The author of this review at the moment knows nothing about coupled elastic rams.

EP_6 (102) is claimed to be a measure of vasomotor tone. It is the level reached by the arterial pressure 6 sec. after it has begun to fall when asystole is produced, or the artery cut off from the heart. It is not clear whether the pressure has levelled off by this six seconds so that it represents a "critical closing pressure," or not. If not, it is very difficult to see why the level after 6 sec. should have any unique significance.

The pressure-flow relations in the veins have been investigated in the animal in connection with the question of increased venous return during inspiration (103). As the aspirating pressure applied to the end of the superior vena cava was increased, there were two stages: a "depleting" stage in which the outflow was proportional to the pressure gradient, and a "collapsed" stage where the outflow was constant and the resistance to flow increased with more negative pressure. In normal respiration the first stage is involved, in deep respiration possibly the second. It seems a little doubtful if the aspiration by physiologically negative intrathoracic pressure can be quantitatively, or perhaps even qualitatively, imitated by negative pressure applied to the end of the veins in open-chested dogs, since the "transmural" pressures, which determine the size of the vessels, will be quite different.

A very original investigation has been made on the intracardiac resistance

to flow in the quiescent and beating turtle heart (104). The resistance is astonishingly high, so that the "internal work" of the heart can be 4.5 to 17 per cent of the external pressure-volume work. The functional importance of the energy required to produce flow of blood through the heart itself has been neglected by everyone else. Results for mammalian hearts will be eagerly awaited.

An interesting lecture on the mechanical peculiarities of the human cardiac pump (105) has been published. In it the law of Laplace (though not attributed to him) is applied, as it was originally to the heart by Woods in 1892, to emphasize the mechanical importance of heart size. It is suggested also that the papillary muscles and the trabeculae corneae (folds of the inside wall of ventricles) play an important role in enabling the heart to empty almost completely. "Without them it would empty only 50 per cent of its contents." This last argument loses much of its force when it is known that this is all that is normally emptied.

Pulse-Wave Velocity and Distensibility of Vessels

The use of retrograde arterial catheterization with electromanometers has made possible the accurate measurement of the pulse-wave velocity in man (106, 107) and in dogs (108) for successive portions of the aorta and arterial tree. There are considerable local differences in velocity, from 5 m. per sec. in the aorta to 8 m. per sec. in the brachial and iliacs while the mean over-all velocity from the heart to the femoral is 4 to 5 m. per sec. The reports agree that the velocity increases as the pulse leaves the aortic arch. There is a deceleration in the vicinity of the diaphragm. Structural differences and branching explain the local changes. The wave changes form as it travels, the pulse pressure increases, so that in dogs (108) it is 35 per cent greater at the end of the aorta than at the valves. This is due to an increase in systolic pressure, the diastolic changing little. The mean pressure, of course, shows little or no change.

The effect of the level of arterial pressure on the pulse wave velocity has been investigated in humans (109). The diastolic pressure was altered by from 45 to 120 mm. Hg by using the cold pressor test, intravenous epinephrine, tetraethylammonium chloride, amyl nitrite, and histamine. In individual subjects the pulse-wave velocity increased with the increasing diastolic pressure. In hypertensives it was higher than in normals, but when corrected to what it would be at a diastolic pressure of 80 mm. it was in the normal range. It is concluded that there is no defect of arterial elasticity, as gauged from pulse-wave velocity, in hypertension, and the increased velocity of the wave is simply due to the increased stretch of the arterial wall by the higher pressure. The pulse-wave velocity, however, was measured from subclavian to brachial, and there might be different results for the aorta.

The effect on the pulse and wave velocity of a saccular aneurism has been studied by connecting an air-cushion chamber to the aorta (110). The pulse pressure was decreased and the dicrotic wave exaggerated, but the pulse-

wave velocity from aorta to femoral was not changed. It is hard to see how a cushion of air in the circuit can really imitate an increase in the volume and distensibility of the aorta, for the inertia and elastic coefficients will be quite different.

Capillary Circulation and Exchanges

For years the term "permeability" as applied to living membranes has been misused. Very often when there was no other ready explanation for phenomena, the physiologist could suggest that there had been a change in "permeability," and while there was no quantitative means of measuring it, this was considered scientifically quite respectable. Indeed, dogmatic teaching about the effects of reversible anoxia, shock and so on as due to increased capillary permeability has been orthodox, though there never was any reliable evidence one way or the other. This practice can no longer be continued without challenge. An event of major importance during the year was the publication by Pappenheimer and his colleagues (111) of his methods and results for the permeability of the peripheral capillary membrane to water, electrolytes, and nonelectrolytes. The method follows logically his equally brilliant previous invention of the "isogravimetric" method in a perfused hind limb. By this method he was able to measure with accuracy the "capillary" pressure, meaning the mean pressure at the vessels where exchange of water was taking place, and from this divide the total resistance to flow into its precapillary and postcapillary components. Having done this, he could measure the rate of gain of weight of the limb when this capillary pressure did not balance the osmotic pressures. The Starling-Landis hypothesis was quantitatively verified, and we had accurate quantitative filtration constants for the peripheral capillary for the first time. Now he has added the measurement of the rate of diffusion through the capillary wall of "foreign" substances added to the incoming stream of perfusate, by a combination of the Fick principle (based on the arteriovenous difference of these substances) and the measurement of their osmotic effect on the movement of fluid. The results establish that the process of diffusion of smaller molecules across the capillary wall is tremendously more rapid than that of filtration. Comparison of the rates of diffusion of different sizes of molecule gives a clear picture of the "molecular sieving" that takes place in the capillary wall.

Not only do we have, for the first time, accurate data on permeability constants and filtration constants, but by a combination of the data on diffusion and on filtration, Pappenheimer succeeds in calculating, not only the fraction of the total area of the wall that is available for these processes, but the size of the pores. This is possible because the diffusion equation and the filtration equation (Poisseuille) contain the radius of the pore raised to a different power. The data are consistent with an average pore size of only about 30 Å with a narrow population scatter. The area available for filtration and diffusion of electrolytes is only about 0.03 per cent of the

total area. It should be a matter of pride to physiologists that, although the physical chemists have for many years been attempting to measure the pore size of their artificial membranes, it remained for a biologist to show how it could be done in unequivocal fashion on living membranes as well.

If the respiratory gases had only these pores through which to diffuse to the tissues, the exchange would be many times too slow to support the metabolism of the cells. However, oxygen and carbon dioxide are much more soluble in lipids than in water (112), and these workers (113) have now shown that lipid soluble substances diffuse much more rapidly through capillary walls. Probably the whole surface of the endothelial living cells is available for this, rather than just the pores.

However, intravenously injected fat is exceedingly slow in reaching the lymph (less than 7 per cent in 8 hr.) (114), although there is a marked stimulation of lymph flow. The passage of respiratory gases across the capillary walls has been studied in the isolated hind limb of a dog (115) when vasoconstriction is produced reflexly or by drugs. Oxygen consumption of the tissues and lactic acid were measured. There is a decrease in the arteriovenous oxygen difference and a decrease in oxygen consumption of the perfused area. There are grounds for thinking that the decrease in oxygen consumption during vasoconstriction is due to a decrease in the area of the capillaries available for exchange. By the use of C^{14}-labelled proteins, it has been shown that the rate of transfer of albumen from circulation to intraperitoneal fluid (experimental ascites) is at least three times as great as that of globulin, in terms of weight (116). Albumin reached equilibrium with plasma in one to two days, globulin in two or more days. For the transfer of glucose from blood to aqueous humour, a phospho-relation mechanism has been suggested (117), because it is affected by alloxan diabetes and increases with the injection of insulin.

The older method of studying "capillary permeability" by observing spreading of injected dye has also been used. Cortisone favours the diffusion of Evans' blue (118) but inhibits the action of testicular hyaluronidase. Testicular extracts, purified to contain hyaluronidase, are not active in affecting spreading (119). "Capillary permeability" is increased in inflammation. Cortisone and ACTH[2] suppress this increase when the exudate is acid, not when it is alkaline (120, 121). A qualitative change in permeability to proteins in the edema of heat is indicated by a change in the albumin-globulin ratio of blood emerging from hot perfused skin (122).

"Capillary fragility" is another measurement where it is hard to know just what is being measured. An extensive research on the suction cup method (ecchymosis test) in man yields many results but few consistent or statistically valid differences (123). It is claimed that Rutin prevents the hemorrhagic phenomena of fulminating renal hypertension, if given 10 days before the production of the hypertension (124). Survival was not affected. This substance is supposed to stabilize the ground-substance of arterioles and precapillary sheaths. The corticomedullary functional tissue of the kid-

ney was strikingly spared. ACTH and cortisone produce only a slight and temporary change in the "capillary resistance" of guinea pigs (125). The swelling of the tail of a mouse following various periods of ischemia (but only with a single occluding pressure) has been examined (126). Some effect is seen after 3-hr. occlusion, but 5 hr. are required to produce marked and persistent swelling. The effects of exposure to altitude on capillary permeability have been observed (127).

It has been found possible to grow new blood vessels *in vitro* in a plasma medium (128), proving that the adult blood vessel epithelium retains the property of forming new capillary tubes even when isolated from the volume and pressure changes of the animal. The specialized vascular system of the ovaries has been studied (129). The arteries are coiled. The capillaries suffer a very great change in size during the cycle, becoming almost sinusoids. The veins have no tunica at all, merely a single layer of epithelial cells. The structure is well adapted for promoting swelling. Premature swelling and follicular rupture follows ligation of the ovarian vein. With the rabbit-ear window, the effect of local irritation by cold or mustard oil and trauma on the spasm has been observed (130). The spread of spasm is affected four to eight weeks after sympathectomy. The electron microscope is beginning to give us information about blood vessel walls and red cell membranes. There are some remarkable pictures from a study of electron microscopy of the heart (131). It is shown by the electron microscope that the cells of "sludged blood" have an amorphous coat, up to 0.5 μ thick (illustrated by remarkable pictures) not seen in normal cells, where the outlines are clear and sharp (132). No statistical data of how many coated or uncoated cells are seen in normal and diseased states is given, or how the sample to be photographed is chosen.

Most of us would have predicted that capillary exchange would continue if the flow were reversed. It is nevertheless reassuring to know that this has been shown (133). In cats, dogs and rabbits an artery was connected to a vein and collaterals were tied off. The blood lost oxygen in its passage and the oxygen consumption fell only from 0.3 cc. per min. to 0.17 cc. per min.

Blood Flow of Limbs and Digits, Muscle and Skin

There has been continued interest in the phenomena of dilation to cold, the so-called "hunting reaction" discovered by Sir Thomas Lewis. Greenfield and his co-workers (134, 135, 136), using the finger calorimeter, have concluded that the reaction is decidedly local, since it is not co-ordinated in neighboring fingers. They find that it is still present when the whole finger tip is infiltrated with anaesthetic, and persists, though modified after sympathectomy, even after time for degeneration. They therefore conclude, contrary to Lewis' opinion, that it is not dependent on an axon reflex. An excellent summary of what is known and some additional observations on sensations of cold and of pain during the hunting reaction has been published in a report from a Government Scientific establishment (137, 138). The ex-

planation of the cyclic vasodilations and vasoconstrictions remains unknown, though obviously the opening and closing of the arteriovenous shunts is involved. Possibly the phenomena could be explained in terms of viscosity changes with temperature, altering the distribution of resistances and pressures and so effecting closure or opening of shunts by "critical closure."

The vascular bed of the stomach also is richly provided with arteriovenous anastomoses like those of the finger (139). Human stomach (necropsy) vessels were perfused and glass spheres of different sizes from 40 to 200 μ were added to the perfusate. Spheres up to 140 μ pass through the shunts, which have been beautifully demonstrated histologically. The size distribution of the outflowing spheres was measured and found to be always the same, though the numbers emerging could be greatly changed by vasoactive drugs. This is taken to mean that the shunts are always either open or closed, and do not hold intermediate sizes of lumen. The effect of electrical stimulation of nerves, cold, epinephrine, ergotoxin, and acetylcholine was studied. All these decreased the total flow of fluid (acetylcholine was inconstant) but increased the number of large spheres emerging. Histamine and alkalinity did the opposite, increasing the flow but stopping the emergence of the spheres. It is clear that whenever the capillary bed dilates, the shunts tend to close and vice versa. Examination of the data shows that this reciprocal relation held even in the case of acetylcholine, which sometimes dilated, sometimes constricted the total flow. In our opinion this could be explained in terms of the pressure at the point where a shunt joined the artery rising or falling below the critical closing pressure of that shunt, as a consequence of changes in resistance of the arteriolar capillary bed that was in parallel with the shunt.

A shifting of blood flow between skin and muscle, called a "borrowing and lending phenomenon," has been postulated (140), as the result of studies of radiosodium clearance from calf muscle, and of toe and finger temperatures. Flow was changed by exercise, direct heat, indirect heat and benzazoline (Priscoline). A reciprocal relation between the changes in skin and muscle flow was found. One conclusion was that the use of benzazoline in intermittent claudication had no physiological basis (but then what has?). The effect of combinations of meals and exercise on skin and muscle flow have been studied (141). Skin flow increased much more than did muscle flow.

Changes in peripheral circulation in heat or cold have been studied in men at sea in natural environments (142). When local temperatures are raised by hot or cold baths, the absence of circulation leads to "more rapid heating or cooling" of muscle (143). This apparent paradox is not real, for the rate of change and the final equilibrium temperature are both changed when the circulation is occluded and need to be distinguished. In acclimatization to heat, the forearm and hand flows are found steadily to decrease (144), a result which is very difficult to interpret in terms of functional advantage to the acclimatized man. For an authoritative discussion of shifts of the

circulation in heat, cold, and exercise, Bazett's paper, posthumously published (145), should be read. In extreme heat, the skin adds histamine to the blood, and this may be an important role in heat prostration with vasodilation (146). The skin of the thigh of dogs was isolated and perfused. When it was raised to 42°C. or higher the concentration of outflowing histamine rose 3 to 10 times. Also the concentration of histamine in the general circulation rose more than could be accounted for without postulating that, in response to the histamine from the hot skin, the body produced excess of this dilator substance.

Most measurements of the flow in limbs in digits are made in connection with peripheral vascular disease and its treatment by sympathetic blockade or sympathectomy. It is puzzling to find that in many cases of intermittent claudication or thomboangiitis obliterans the flow is not always markedly reduced. The flow of the great toes was below normal in cases of peripheral arteriosclerosis, Raynaud's disease and a single case of scerloderma, but normal in thrombophlebitis and acrocyanosis (147). Cold and cyanotic extremities are often observed in schizophrenia (148), and, though forearm flow is normal, hand and finger flow is decreased. There is also a delay in reflex vasodilation. There are many enthusiastic reports of the clinical benefits of sympathectomy (149, 150, 151), but most measurements of flow show a return of tone and peripheral resistance in a few days (152, 153), e.g. following lumbar sympathectomy for hypertension here. In limbs with arterial obstruction, a method has been devised by which the resistance of collateral pathways can be estimated from the change in local arterial pressure in reactive hyperaemia (154). Again it was found that sympathectomy reduced the collateral resistance greatly but it returned to the original level in a few days. Study of the local pressure pulse, by electromanometer and arterial catheter, in obstructive arterial disease shows that the pulse pressure is reduced more than the mean pressure (155). The changes in pulse pressure are explained by a theory that the collateral circulation acts as a low-pass filter. The flow in the affected limbs was usually greater than in the normal side! Oscillometric deflections therefore would give no indications of resting blood flow in such cases. Intra-arterial histamine injections have been tried for occlusive disease (156), and eventual benefits are claimed though at the time of injection the flow in feet and toes, judged from skin temperatures, was further impaired. It is suggested that the development of arteriovenous anastomoses is thus encouraged. One case of intermittent claudication successfully treated with hexamethonium bromide has been reported (157).

The physiological effects of arteriovenous anastomoses have been measured on both sides of the Atlantic. In one case of femoral aneurysm and one in the thenar region, blood flows of foot and of fingers were measured plethysmographically (158). Arterial pressure in the distal arteries was lowered but flow was normal or greater than on the normal side. On closing the fistula, digital arterial pressure rose and flow increased. The changes in flow reported, however, seem hardly significant in view of the great fluctu-

ations that are seen normally. The other research was on surgically-created femoral arteriovenous fistulae, and the dogs were deeply anaesthetized (159). On opening the fistula the cardiac output rose an estimated 30 per cent, the arterial pressure proximal to the fistula fell, and venous pressure in the neighbourhood rose markedly. All these phenomena are those that would be predicted by elementary haemodynamics, which would suggest that the chief abnormality with arteriovenous fistula will be an extra load on the heart, rather than any local peripheral ischemia.

The blood flow through the normal human knee segment has been measured plethysmographically for the first time (160), and proves to be moderately low (1 to 4 ml. per 100 ml. per min.). Dissection of knees shows that 20 per cent is skin and subcutaneous fat, 25 per cent muscle and 55 per cent bone and joint structures. There was a large increase in flow when local temperature was raised above 35°C. Studies with epinephrine iontophoresis suggested that deep and superficial flows might be thus separated. At 30°C. the deep component accounted for two-thirds of the total, less at 35°C.

The blood flow in the umbilical cord must certainly be considered as peripheral. Three papers (161, 162, 163) describe its measurement in foetal sheep and guinea pigs. The foetus is enclosed in a plethysmograph, and it is possible to occlude the venous return without interfering with arterial inflow. There is a marked difference between the flows in the two species, there being four times as much in the sheep, reckoned per kilogram of foetus.

We should take warning that flushing of the skin does not necessarily mean an increase of flow. A nicotine alcohol tartrate, which is used as a peripheral dilator for both coronary and peripheral vasodilation, proved to have no effect on arterial pressure, finger blood flow, heart rate, or flicker-fusion photometric measurements (164). Yet it produced a marked flushing. Apparently, like histamine, it may dilate capillaries but at the same time constrict arterioles.

Nervous Control of Circulation and Buffer Reflexes

It is astonishing that since Claude Bernard discovered the function of the peripheral vasomotor nerves more than 100 years ago, there have been practically no quantitative measurements of the effects of their stimulation on the resistance to flow. The reason appears to be that stimulation with the usual stimulators destroys the function of these nerves very soon and no consistent results worth publishing were achieved. A low-voltage flat-topped stimulus of very long duration (15 msec.) has to be used. The complete pressure-flow curves for the rabbit ear (Gaddum type of preparation) with stimulation at different frequencies have now been obtained (165). The maximum effect is with a frequency of 15 or 20 per sec., higher frequencies giving less constriction, probably because of Wedensky-type inhibition at the smooth muscle effector organ. As the frequency increases from zero, the pressure-flow curves pass from an approximate straight line, passing almost through the origin, to curves convex to the pressure axis, or sigmoid,

with an increasing zero-flow intercept (critical closing pressure). A very important deduction from these results is that the effectiveness of a given degree of activity in the sympathetic nerves in reducing the blood flow is greatly enhanced when the arterial pressure level is reduced. For example, impulses at 15 per sec. may reduce the flow 50 per cent at a pressure of 100 mm. Hg, but to zero when the mean pressure is 60 mm. Hg. The application to the problem of vasomotor tone in low arterial pressure shock is obvious. A very similar research has been on the blood flow of the skinned hind limb of a cat, flow being recorded by a drop recorder (166). Stimulation of the sympathetic nerves had no influence at 0.5 per sec., the effect then increased to a maximum at 10 to 15 per sec. The resistance to flow was then increased 10 to 12 times. There was a decline of effect at frequencies higher than 30 per sec. This is related to the transmitter mechanism at the muscle. The physiological discharge rate in the sympathetic was then deduced by comparison with the results by physiological stimulation. The author finds that the physiological impulse rate seldom surpasses 6 to 8 per sec., and normal tone corresponds to 1 to 2 per sec., this result agreeing with older work of Bronk. The role of dilator sympathetic fibres is investigated by blocking with ergotamine. After dilator drugs have been given, the maximum constriction by stimulation is less, and not reached until a higher frequency. Sympathetic vasodilator fibres to the tongue of the cat have been similarly investigated (167). Cholinergic fibres are present, because acetylcholine is detected in the outflowing blood. Antidromic stimulation of posterior roots results in a vasodilation in skin (168). The flow from a cutaneous branch of the saphenous vein increased fourfold. Bioassay for histamine proved that this was released at a concentration 30 or 40 times normal. Antihistaminic drugs diminished or abolished the effect on blood flow, though they did not affect the vasodilation produced by a local injection of acetylcholine. This verifies the theory of Sir Thomas Lewis that such antidromic stimulation produces vasodilation by release of histamine-like substances.

There has been a great revival of interest and investigation of the carotid-sinus baroreceptors, led by the Scandinavian group (169 to 173). Their beautiful technique of recording the action currents of single fibres from these receptors (which they can distinguish from the impulses from chemoreceptors) has made possible considerable advances. An important discovery is that vasopressor and dilator drugs act directly on the sensitivity of the receptors by altering the stretch of the wall in which they lie. This effect has been analyzed biophysically by related determinations of the pressure-volume curves of the sinus-aortic vessels, normally and under the influence of the drugs. For details these important papers should be consulted. The discoverer of the baroreceptors is also working on this aspect (174) (apparently independently, for there is little reference to the other work). Here the arterial pressure response of the animal is used rather than the recording of action currents. The drugs were injected into the adventitial space sur-

rounding the vessels of the sinus, and responses were obtained with very low concentrations.

What has been considered to be the homologue of the mammalian carotid body and sinus mechanism has been described in a lizard (175). The clinical importance of the carotid sinus has been assessed, with reports on 20 cases (176). An influence of the carotid sinus baroreceptors on gastrocnemius muscle contraction in the cat has been claimed (177), lowering the carotid sinus pressure increasing the contraction to electrical stimulation. This is attributed to hormones liberated by local adrenergic nerves. Care has to be taken in experiments, where the carotid sinus is apparently isolated, that account is taken of the vascular communications with the vertebral circulation, which are different in different species. These communications have been carefully demonstrated (178). In rabbits with the carotid sinus and aortic nerves sectioned there is still a cardiac inhibitory effect of injection of pressor drugs (179, 180). This is attributed to depressor fibres in the vagus trunks.

There are many other regions where receptors exist that initiate reflexes controlling the circulation. Among these are the heart and lungs (181). The data suggest that there are pressor receptors in the wall of the left ventricle and in the lungs also (182). However, these have mostly been demonstrated by chemical stimulation rather than by pressure changes. The Pacinian corpuscles have also long been known to be baroreceptors. A study of the adaptation and accommodation of these has been made (183). The distribution of vasoconstrictor fibres along the small intestine has been studied by electrical stimulation (184). Cross-circulation experiments have indicated that baroreceptors exist in the wall of the descending aorta about 3 cm. from the renal arteries, close to the arteries to the suprarenals (185).

The systemic pressor response to increased intracranial pressure has long been known, and attributed to anaemia, asphyxia, or anoxia of the brain. It has now been shown that it occurs when the pressure is raised directly through a tube inserted in a trephined hole in the cranium (186). The rise of systemic arterial pressure has a lag of only a few seconds. Carotid sinus denervation increases the response. In contrast, hypoxia gives a fall of arterial pressure. These facts do not agree with the explanations that cerebral anoxia is the cause of the phenomena. The existence of a baroreceptor in the cranium is suggested, stimulated normally by a rise of pressure in the blood vessels. An increased intracranial pressure would then be expected to act on the receptor in the same way as a fall of arterial pressure (i.e., the vessel walls would be relaxed), and the vasomotor centre would respond by raising the arterial pressure. On the other hand, another group of workers have been using a preparation where the brain is isolated from the body of dogs except for nervous connections in the spinal cord (187, 188). They find no responses to raising the cerebral vascular pressure, but marked pressor and depressor responses to vasoactive drugs. The response

to most pressor drugs is a peripheral hypotension and to depressor drugs a hypertension. They conclude that the receptors are chemoreceptors rather than baroreceptors, but they mediate vasomotor reflexes.

An interesting finding in unanaesthetized dogs is that the change of heart rate during respiration, and with epinephrine, norepinephrine, and acetylcholine was directly proportional to the pressure gradient in the venous system, from leg vein to right atrium (189). No relation was demonstrable between the level of atrial pressure and the heart rate. It is concluded that not the atrial pressure, but the velocity of filling of the atrium (or the pressure gradient) is the adequate stimulus for the Bainbridge reflex.

Local reflexes from the veins and arteries have often been discussed without definite evidence. A study of the vasomotor effects of electrical and chemical stimulation and of distension of the femoral vein, artery, and of muscles, failed to reveal any reflex changes in flow in the opposite leg measured plethysmographically (190). This failure should not be taken as final for the animals were anaesthetized, and also if such reflexes were mediated by a nerve plexus on the wall of the vessel, conduction might have been blocked by some of the manipulations. Also it might be that there are ipsilateral local reflexes rather than central, and these were not investigated.

Pressor and depressor effects of pain have been studied in unanaesthetized rabbits and cats by stimulation of the dental pulp (191). (The title calls this "presumably painful"—most of us would be quite sure it is.) In the unanaesthetized animal there was a rise of arterial pressure, decrease in leg volume, decrease in kidney and spleen volumes, and contraction of the nictitating membrane, all of which would be imitated by epinephrine. In the anaesthetized animal the effects were opposite, i.e., mainly depressor, except that leg volume decreased in both cases. It is concluded that there are both pressor and depressor effects of stimulation, the pressor ones arising from pain perception, which is eliminated by anaesthesia. It does not seem quite logical to regard this as final proof, since perception of pain is not the only pathway blocked by anaesthesia.

Under the heading of this section should be included studies of positive G upon circulation (192 to 196), of negative G (197, 198), and of the Valvalva manoeuvre (199, 200). Study of these is a useful way of showing differences between normals and those in heart failure, hypertension, or with mitral stenosis. However, the physiology is so complicated and detailed that no comments can be made in a brief review.

Hypertension

The reviewer read, with varying degrees of understanding or critical judgment, over 100 papers published in the last year on the subject. Only a very few will be referred to because they seem to offer new ideas or reach conclusive proof. It seems quite impossible to review the rest in any sensible categories, for the experimental arrangements and multiple operations on the animals are complicated, the variety of drugs given great, and the

results confusing. It does not seem worth even listing them, for those in the field will be acquainted better with them than this reviewer, and possibly can deduce some principles from them.

To one who, like the author, is not actually engaged in research on the baffling problem of essential hypertension in humans, it is astonishing that the great bulk of research time and money is being spent on continued investigations of the role either of the kidney or of the nervous system in the production of hypertension. The two schools of enthusiasm each have shown convincingly that the other group is pursuing an incidental factor and not the true etiological one. To the rest of us it looks as if they are both right in this. Their preoccupation makes both camps apparently blind to the obvious suggestive evidence that the place to look is the adrenal cortex, though the mechanism is as yet completely obscure. This evidence is, of course, the hypotension of Addison's disease, the hypertension produced by DCA,[2] the disturbance in hypertension of the sodium and potassium balances, the modification of renal hypertension after adrenalectomy, and the stress-syndrome as a predisposing factor in human hypertension. The difficulty seems to be that those who are familiar with haemodynamics are mostly scared of plunging into "endocrinology," while endocrinologists mostly don't know a thing about haemodynamics.

Therefore forgetting renin, angiotonin, vasopressin, serotonin, hypertensin, and all the other vasoactive agents, neurogenic versus renal hypertension, and the effect of all the different methonium compounds, 1-hydrazinophthalazine and the veratrum alkaloids on unilateral renal constricted, then nephrectomized, and subsequently denervated rats, and not distinguishing between lumbar sympathectomies and splanchnicectomies, the author heaves a sigh of relief and turns to a few papers that seem to point conclusively towards the dominant role of the adrenal gland, probably the cortex.

First, analyses have been made of the cations and water in the wall of renal arteries (with the adventitia stripped off), atrium, bladder, psoas muscle, and frontal lobe of the brain, using human necropsy material 5 to 7 hr. after death. There is a significant increase in water and in sodium, on the basis either of wet or dry weight. This amounts to about 17 per cent in 17 hypertensives compared with 15 normotensives. It was unrelated to edema in the patients. The amounts of potassium and magnesium were normal (201). The authors point out that if an arteriole, of wall thickness 10μ and lumen diameter 10μ were to have its wall swell by 13 per cent by reason of sodium retention, the new wall thickness would be $11.5\ \mu$ and the lumen diameter reduced to 9μ. By Poiseuille's law, the resistance to flow would thus increase by 50 per cent. (It is to be noted, however, that this calculation depends on the assumption of some particular restriction on the swelling. For instance, if the outside circumference of the wall were undistensible, even greater reduction in lumen size would take place; if it were unrestricted, and all tissue swelled alike, the lumen would increase as does that of a metal washer when heated. The theory depends therefore on

there being a gradient of swelling through the vessel wall, and it is to be hoped the authors will show that the adventitia has retained less sodium and swelled less. The authors suggest that the benefit of sodium deprivation diets is that about 200 m.eq. of sodium are lost from the body before balance is attained. Others had shown that sodium accumulated in experimental hypertension in animals, but the suggestion as to swelling of arteriolar walls in increasing peripheral resistance seems original and stimulating.

In rats made hypertensive by subtotal nephrectomy (a figure eight ligature followed by contralateral nephrectomy) the total body sodium increased from the normal of 1.29 mg. per gm. to 1.67, while the total nitrogen and K^+ were unchanged (202). The plasma sodium remained within normal limits. The increased intracellular penetration of sodium must be compensated by a change in pH and protein binding or exchange with, for example, magnesium. This has not yet been investigated.

Several researches on the low sodium rice diets (203, 204, 205) have shown that the important feature of the diet is sodium restriction. Resins that are now used in other diets selectively remove sodium more than other ions (206). The muscular weakness sometimes encountered might be due to magnesium depletion (207). Again, low sodium diets do not lower the arterial pressure of renal hypertensive dogs, but if the plasma sodium is lowered from the normal of 140 to 150 m.eq. per l. to 115 or 120 by intraperitoneal lavage, there is a sustained reduction to normotensive levels (208). The same procedure on normotensive dogs did not alter the arterial pressure, so this discounts the accompanying lethargy, weight loss, and anorexia as an explanation.

On the other hand, deprivation of potassium leads to a slow depression of arterial pressure, and the fall is prevented by simultaneous deprivation of sodium (209). The reaction to vasopressor drugs is reduced to half what it was (210). The hypertension produced in rats by DCA is increased if potassium is fed, and abolished by deprivation of potassium (211). (Curiously, while excess potassium increases DCA hypertension, it protects the animals from the usual vascular damage.) The depressed reactivity on low potassium diets is abolished within an hour when the ion is restored (212). It is clear then that sodium and potassium are antagonistic in these relations.

The most conclusive evidence that the adrenals are involved, even in so-called "renal hypertension" comes from two papers in *Clinical Science*. Hypertension was produced in rats by placing a clip on one renal artery (213). After eight weeks the clipped kidney was removed, and hypertension continued in about half the rats. If the untouched kidney was then removed, the arterial pressure returned to normal in these animals. The continued hypertension must therefore have been due to damage produced in the unclipped kidney (which damage was obvious, while not seen in the clipped kidney). It is concluded that there may be two pressor factors concerned in renal hypertension, one from an abnormal kidney (clipped or damaged by hypertension), one from an extrarenal source. The abnormal kidney may

stimulate this extrarenal factor directly, or it may prevent the opposite and initially normal kidney from eliminating this extrarenal factor. For the extrarenal factor, the author suggests the adrenal gland through its effect on salt balance.

The difficulty with such experiments where both kidneys are removed is, of course, the complete loss of renal function and the rapid deterioration of the animal. It had been found previously that parabiotic rats (skin joined at 18 to 24 days) would thrive and grow with their circulations interconnected, and that if total nephrectomy were done on one member, the kidneys of the other took over their functions adequately. It has now been shown that the nephrectomized member becomes hypertensive (214), while the other does not. Moreover, arteriolar lesions occur in the nephrectomized member, not in the other. If now, the adrenals of the affected member are totally removed, the hypertension is abolished. With these and other related experiments, the author shows with logic that seems inescapable that the hypertension must be due to a pressor factor from the adrenals, which is normally eliminated or neutralized by the kidney. The impact of these two papers is greatly enhanced in that the editors have allowed the authors to deliver successive blows of logic, by describing each experiment, its results and the alternative explanations before turning to the next experiment, which is called for by logic to eliminate some of the possibilities. The modern rigid mould of "method, results, and discussion" including all the experiments at once tends to detract from the meaning of many researches.

Others have shown that for hypertension in rats all that is needed is a young animal, adequate sodium, and the removal of one kidney (215). There have been other papers concerned with the hormonal factors in hypertension. Ascorbic acid or cortisone inhibits DCA hypertension in rats, but does not prevent the renal lesions. If the adrenals are removed, no lesions occur from DCA (216). This is interpreted to indicate that ascorbic acid increases the liberation of cortisone by the gland, and this is responsible for the lesions. Ascorbic acid also prevents the hypertension in rats long exposed to cold. The same group of workers has shown that ascorbic acid can also inhibit the hypertension due to excess sodium chloride in the drinking water and from renal compression (217), although the arterial pressure lowering is not permanent.

A contrary argument has been advanced (218). Soffer showed that patients with Cushing's syndrome have an abnormal response to salt loading and to DCA (if essential hypertension involves adrenal cortical hyperfunction, with respect to electrolyte balance, it is argued, patients with the disease should give a positive Soffer test.) Yet 9 out of 10 patients showed the normal response. The weak point of this argument is, of course, that the abnormality of cortical function in hypertension need not be the same as in Cushing's syndrome (it would be most unlikely if it were).

Going one step further back in hormone complications, it has been concluded that the low arterial pressure, the atrophy of the heart, and inability

of the heart to hypertrophy when the aorta is narrowed in hypophysectomized rats are not due to atrophy of the thyroids and adrenals (219). Growth hormone prevents the atrophy and hypotension of hypophysectomy (220).

One case has been reported (221) of a normotensive subject with a family history of hypertension, who developed a hypertensive response to DCA several months before the essential hypertension appeared. When it was developed, the benzodioxane test for pheochromocytoma was negative.

Somehow or other the adrenal cortex must be to blame in hypertension.

Conclusion

Only a small fraction of the papers published in any one year, that contain facts or theories about the peripheral circulation, can be reviewed by any one person. If the title does not suggest this topic, it will usually be missed, whereas almost any paper in physiology contains some reference to circulation. In completing the review one feels in the mood of the writer of the Gospel of St. John, and saying

> There are also many other things that physiologists did, touching the circulation, the which, if they should be written every one, I suppose that even the world itself could not contain the books that should be written.

The hard secretarial work of Mrs. D. Walls and of the library staff of the Medical School, in connection with this preparation of the review, is gratefully acknowledged.

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HEART[1,2]

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Conduction System

Despite the protest of Glomset & Cross (1) that it is folly to develop theories concerning mechanisms of impulse conduction in cardiac muscle which are based on "a nonexistent conduction system," investigators continue to describe the anatomy and development of a specialized pathway. Thus, Lenègre & Chevalier (2) present a new method for its study in man, using longitudinal rather than transverse sections, and Widran & Lev (3) have dissected the atrioventricular node, bundle of His, and the bundle branches in 41 human hearts. Microscopic studies by Franco (4) have revealed the presence of several atrial conduction paths. Hukuhara & Yokoyama (5) have described automatism of the sinoatrial ring of the homeotherm heart (rabbit, dog, cat).

These anatomic studies have been supplemented by embryologic observations. Patten (6) has recorded the onset of the heart beat in the chick embryo before specialized conducting tissue or nerve mechanisms could be detected. Field (7) conducted an ontogenetic study of its development in the heart of sheep, using embryos which varied in size from 4 mm. to birth and established the appearance of structures in the following order: atrioventricular bundle, atrioventricular node, Purkinje fibers and sinoatrial node. Truex & Schwartz (8) have demonstrated in human fetuses myocardial sinuses and veins which lie immediately adjacent to the atrioventricular node and His' bundle, and suggest a possible role for these venous channels in the dissemination of toxins into the common bundle.

Contractile Elements

Physiology.—The factors which control or modify the reactions of isolated contractile elements of muscle continue to stimulate interest. Kisch & Bardet (9) have studied heart muscle by electron microscopy. Szent-Györgyi (10) has reviewed his concept of the mode of interaction of actomyosin, ATP, and various ions, and the role of the wave of excitation in initiating the contractile process. With Hadju (11) he has re-explored the "staircase" phenomenon of Bowditch and observed its abolition by low temperature, low potassium to sodium ratio, serum, desoxycorticosterone

[1] This review includes the period from July 1951 to June 1952.

[2] The following abbreviations are used in this chapter: ECG (electrocardiography or electrocardiogram); VCG (vectorcardiography or vectorcardiogram); EKY (electrokymography or electrokymogram); BCG (ballistocardiography or ballistocardiogram); ATP (Adenosinetriphosphate).

and also by digitalis glycoside (12). They postulate that these substances modify the selective permeability of the membrane, thus establishing a new intracellular ionic atmosphere. The influence of divalent ions, rather than sodium and potassium, on the contractile process has been emphasized by Bozler (13) and Bowen (14, 15), and a normogram relating various ions to cardiac contractility has been presented by Salter & Runels (16). Furthermore, Bowen (17) has suggested that digitalis influences the contractile process by either altering the contractile proteins or the union between ATP[2] and myosin B. The varying concentrations of actomyosin in the individual chambers of the dog heart are related by Ranney (18) to the work performed.

Several investigators have called attention to the similarities between skeletal and cardiac muscle (19, 20). With these similarities in mind, the series of papers by Polissar (21 to 24) warrant consideration since he has applied concepts of polymer chemistry and physics to explain various familiar phenomena of muscle physiology.

Metabolism.—The complex chemical reactions and the catalysts which govern the release of energy for contraction are also being explored. Thus, mitochondria have been shown to contain the complete enzymatic apparatus for implementing the reactions of the citric acid cycle and for generating oxidatively energy-rich phosphate bonds. Paul *et al.* (25) have demonstrated that the cyclophorase-mitochondrial system of the rabbit heart is similar to other mitochondrial systems, but is characterized by an unusually high level of magnesium. A number of experimental studies deal with glycogen which is the primary source of energy for contraction of cardiac muscle. Seifter (26) described a reversible increase in cardiac glycogen of rats deprived of potassium for 7 to 77 days. The total carbohydrate content of heart muscle in guinea pigs is increased more following intraperitoneal fructose than glucose (27). The glycogen content of mammalian hearts is reduced following anoxia (28, 29), following burns and histamine intoxication (30), and in shock (31). Cavert & Johnson (32) have described the metabolism of isotopic lactate by the blood-perfused isolated heart. Mulder and others (33) have recorded the effect of an injection of glucose, and insulin or both on the phosphate fractions and glycogen content of the dog's heart. Effects of anoxia on myocardial metabolism, other than those mentioned above, have been investigated (34 to 37).

Robertson *et al.* (38) have studied the alterations in distribution of water and electrolytes induced by epinephrine and arterenol in cat heart muscle. Iseri *et al.* (39) describe a reduction in the potassium content of cardiac and skeletal muscle in patients dying with heart failure. Since present methods of partitioning water and electrolytes between cells and the surrounding medium are usually ingenious but roundabout approaches to a difficult problem, results based on these methods must be interpreted with reserve. The effects of sulfur-containing amino acids on myocardial contractility (40) and cardiac glycosides on the myocardial respiration (41) have been described.

Electrophysiology.—It is difficult to dissociate progress and understand-

ing of cardiac electrophysiology from advances in the knowledge of the physiology of other excitable tissues, therefore attention is called to recent basic studies of ionic transfers during excitation and conduction. These include the role of alterations in permeability to sodium in effecting nervous conduction (42), the transmembrane inward and outward fluxes of sodium and potassium during rest and activity (43), and the elucidation of laws which govern the movement of ions to produce electrical activity (42, 44, 45, 46). Draper & Weidmann (47) and Weidmann (48) have recorded resting and action potentials from the "false tendons" (bundles of conduction tissue) of the dog and kid heart. In contradistinction to the theory of simple depolarization of the membrane postulated by Bernstein, they conclude that electrical activity in heart muscle cells, as in other excitable cells, is associated with a transitory reversal of potential difference; the rhythmicity of the heart is accounted for by quantitative changes in relative permeabilities of the membrane to various ions, particularly sodium. Their data suggest that the rising spike of the action potential in cardiac muscle is brought about by increase in permeability to sodium. Cranefield *et al.* (49, 50) have described alterations in sodium permeability and electrical resistance, using potentials recorded from the injured wall of the turtle heart and have noted seasonal variations in resistance of the injured wall. Fingl *et al.* (51) measured membrane resting and action potentials in three to eight day chicks, and could not demonstrate any increase in sensitivity to chemical mediators after the establishment of innervation. Woodbury & Hecht (52) have recorded the modifying influences of digitalis glycosides on the membrane resting and action potentials of the frog heart. The induction of ventricular fibrillation is related to ventricular vulnerability by Hoffman *et al.* (53) and to the duration of stimulation by Vanremoortere & Dalem (54).

Heart Rate

The effects of temperature on heart rate stimulate reinvestigation. Badeer (55), using thermocouples for recording, has repeated Starling's experiments and confirmed that there is a linear temperature-pacemaker relationship from 25° to 38°C. Scott & Reed (56) have shown that the induction of nodal rhythm by cooling the sinoatrial node may be modified by carotid sinus stimulation. Tanner (57) emphasizes that the difference in heart rate observed in healthy young males at rest may have various causes, but that the blood temperature is probably the most significant single factor. Smith (58) has elicited five different temperature-pulse rate curves, using frogs obtained at different monthly intervals, and presents evidence to indicate the role of endocrine secretions in influencing this relationship. The return of heart rate and other cardiocirculatory functions to normal during rewarming has been shown to retrace the path observed during cooling (59); the use of intracardiac catheters during cooling apparently favors the onset of ventricular fibrillation. Lyman (60) has extended previous observations on the effect of carbon dioxide concentrations upon the heart rate of the hiber-

nating animal and its arousal from hibernation. The effect of exercise and position on heart rate has been investigated in normal subjects (61, 62) and in patients with left heart failure (62). Other factors which influence the heart rate will be discussed under the sections on Cardiac Innervation and ECG[2].

Cardiac Innervation

Bartorelli & Folli (63) have concluded that the phenomenon of vagal escape is primarily related to the diphasic response (myocardial and cholinergic) elicited by acetylcholine. Various effects of carotid sinus stimulation have been described in man. Linenthal (64, 65) has introduced a simple method for controlled application of external pressure to the carotid sinus and Franke (66) has recorded circulatory changes following bradycardia produced by carotid sinus stimulation. Hellerstein *et al.* (67) have used a continuous ECG to trace the progressive changes in pacemaker and conduction during conversion of a supraventricular tachycardia to normal sinus rhythm.

In animals, McCubbin & Page (68) have demonstrated that neither increased heart rate nor cardiac output are primary mechanisms in chronic experimental neurogenic hypertension produced by section of buffer nerves. Youmans *et al.* (69) attribute the cardioinhibitory responses, which persist in the rabbit after section of both aortic nerves and removal of both carotid sinuses to depressor fibers in the uncut vagi. They also showed (70) that after removal of all known depressor pathways, vasopressin elicits in the dog a severe bradycardia, which they believe due to inhibition of cardioaccelerator activity. Jullien & Ripplinger (71) have observed remarkably constant negative tonotropic action following stimulation of the vagus nerve in deep sea fishes, which was not reproduced by acetylcholine nor inhibited by a variety of topically applied drugs. Vagal responses were modified by Young *et al.* (72) in the anesthetized dogs, by varying pH and the composition of inspired gas mixtures, and Anand (73) elicited a greater inhibitory effect upon the frog heart following vagal stimulation when temperature was high than when it was low. Nelemans (74) has analyzed the effects of faradic stimulation of the frog heart.

The reflex of von Bezold, i.e., bradycardia, hypotension and depression of respiration, can be elicited by a wide variety of drugs, including the veratrum alkaloids, cinchoninic acid derivatives, and germitrine (75, 76), although different sensory receptors and several mechanisms may be involved. Dawes *et al.* (77) review the respiratory and circulatory reflexes elicited by the veratrum alkaloids and some derivatives, and Swiss & Maison (78), in a series of cross-circulation experiments, dissociated the effects of these alkaloids mediated through the head from those mediated through the body; their experiments confirm that the bradycardic action of veratrum derivatives is mediated via the vagus nerve.

Cardiac Performance

Hemodynamic principles.—Wiggers (79, 80) has reviewed the results of 33 years of animal experiments in his laboratory. Although it is recognized that acute experiments, which he describes, do not permit adaptive mechanisms to evolve, nevertheless the same general hemodynamic principles apply to the evaluation of results of the chronic disorders currently under investigation in man. He concludes that, under controlled ordinary conditions, the filling pressure of the ventricle in diastole will determine fiber length and the strength of the subsequent contraction; this relationship, however, is not maintained under the conditions of pericardial effusion, premature ventricular beats, and ventricular tachycardia. Furthermore, he stresses that under a given set of experimental conditions, the need for equal states of myocardial responsiveness must be taken into account before concluding that the law of initial length does, or does not, apply. His comments pertain to the results reported in the papers which follow. Lagerlof *et al.* (81) in their experiments on the effects of change of posture (and of venous return) illustrate cardiac behavior in accord with Starling's Law. On the other hand. Little *et al.* (82) using a modified heart-lung preparation, found that left ventricular output may vary oppositely to left ventricular diastolic pressure; it may be questioned whether the nature of these experiments (induction of heart block to cause bradycardia) may not have altered myocardial responsiveness. Rushmer *et al.* (83, 84, 85) have used cinefluorographic angiocardiography to record the motions of the ventricular chambers during the cardiac cycle and determined the relation between effective filling pressure and the diastolic size. However, Ring *et al.* (86), on the basis of their experiences with electrokymography, conclude that records obtained in one plane may be inadequate to indicate changes in volume. Ferguson *et al.* (87) determined stroke volume by T1824 dye injection and the pressure pulse methods, and concluded that following intravenous infusion, no consistent relationship could be demonstrated between stroke volume and the effective end-diastolic pressure in the left ventricle.

Burch *et al.* (88), in a theoretical discussion requiring many simplifying assumptions, consider the human heart as a pump in normal and disease states. Opdyke (89) has presented a new method for studying the relaxation process of the ventricles, using a donor dog to perfuse the coronary arteries of the isolated heart. McMillan *et al.* (90) have photographed the movements of normal and diseased aortic and pulmonary valves obtained at autopsy. Little (91) has analyzed the effects of atrial systole on closure of the atrioventricular valve under varying degrees of venous return and states that, in the absence of atrial contraction, blood regurgitates during systole through the atrioventricular valve. The observations made in the reviewers' laboratory on patients with atrial fibrillation, i.e., that atrial pressure tracings almost invariably reveal evidence of tricuspid insufficiency, add interest to these experiments.

Cardiac output.—Considerable interest is currently focused on methods for measuring cardiac output. The direct Fick method continues to be widely used and supplies accurate data if the conditions necessary for its application are observed. Attempts by Grossman *et al.* (92) to substitute *p*-acetylamino-hippurate for oxygen as the test substance may simplify the analytic procedures but introduce a new group of experimental variables. The limitations of the direct Fick method (inability to detect fleeting changes, need for the steady state, mixed venous blood sampling, and oxygen analysis) stimulate the search for new techniques. The Stewart-Hamilton "dye dilution" method is in the foreground, and the dye analyses have been simplified by means of oximeter cuvettes (93, 94) and photoelectric recording apparatus (95). Good correlations between direct Fick and dye methods have been reported in normals (96, 97), and in subjects with mitral valve disease (98, 99). However, the dye method has been described as unreliable if the cardiac output is too low (100), and higher values have been recorded by this method than by the direct Fick in the normal dog (95), and in patients with severe mitral stenosis (101). It seems worthy of note that in many reported "good correlations" tabulated data show considerable spread, and experimental conditions do not appear to be adequate for valid application of the Fick principle. Furthermore, there is little information available regarding such correlations when the cardiac output is changed and maintained at a new and steady level in the same individual. The dye dilution technique has been used in the attempt to evaluate changes in cardiac output following administration of plasma expanders (102) and following myocardial infarction (103).

Substances other than dye have been employed in dogs as indicators for the calculation of cardiac output. Good correlations have been reported in comparing the results obtained simultaneously with P^{32} tagged red blood cells and T1824 (104), and human serum albumin tagged with I^{131} and the rotameter (105). Using controlled experimental conditions, Longino & Gregg (106) could only demonstrate a fair correlation between the pressure pulse contour and direct rotameter methods for determination of cardiac output.

Taylor & Tiede (107) have examined the validity of the cardiac index as a standard, with particular reference to its utility in predicting cardiac output of individuals, and conclude that as determined by four commonly used methods, it is a physiologically meaningful measurement. Taylor *et al.* (108) believe that the increase in cardiac output observed following weight gain in man is due to the addition of fat-free tissue. Kenney *et al.* (109), also using the direct Fick, could not demonstrate any change in cardiac output following carotid sinus stimulation in the dog and conclude that this method is inadequate to reveal transient, beat to beat, effects.

Coronary Circulation

Anastomoses.—By many ingenious types of perfusion experiments, the

coronary arteries have been demonstrated to have anastomotic channels. Wiggers (110) questions their functional significance and concludes that in the normal dog, and presumably in man who has a poorer collateral supply, the coronary arteries are functionally, albeit not anatomically, end-arteries. However, with slow occlusion, these potential intercoronary and extracoronary channels can develop into functioning communications, due to establishment of favorable pressure gradients and anoxia. Formation of intercoronary anastomoses has been shown to be stimulated by anastomosing the internal mammary artery to the ventricular myocardium (111). Graham & Williams (112) describe a new method for direct, simultaneous, and continuous measure of total coronary flow and venous return in the open-chest dog, and conclude that coronary flow varies directly with increase in arterial blood pressure and cardiac output.

Flow.—Bing (113, 114) has reviewed the results obtained from studies of the coronary circulation in man, utilizing catheterization of the coronary sinus. By this method, coronary flow is calculated to represent 5 to 10 per cent of the cardiac output. He points out that the metabolic demands of the heart are fulfilled by a large extraction ratio for oxygen rather than a large blood flow. Foltz *et al.* (115), using coronary sinus catheterization in dogs, conclude that epinephrine and norepinephrine have similar effects on coronary blood oxygen extraction. Sherrod (116) has evaluated the effects of cardiac glycosides on the coronary blood flow. The validity of these experiments rests on the premises that coronary sinus outflow represents a fixed fraction of the total flow of the left coronary artery and that coronary sinus outflow is an index of the total coronary circulation.

Innervation.—The problem of coronary "spasm" is stimulating further discussion and investigation. Pickering (117) adduces evidence that many instances of alleged coronary vascular spasm seem explicable on other grounds, chiefly arterial occulsion. Wiggers (110) can find no conclusive evidence that drugs increase the calibre of potential intercoronary communicating vessels nor evidence for intercoronary reflexes. On the other hand, Arnulf (118) has photographically demonstrated dilatation of the coronary artery after section of the periaortic plexus, and Lu (119) has described improved myocardial contraction as well as constriction of the coronary vessels following administration of posterior pituitary extract to the perfused rabbit and dog heart. The effects of various drugs upon isolated coronary vessels of man and swine have been studied by Smith *et al.* (120) by means of an improved angioplethysmograph.

Coronary occlusion.—Using the polarographic method of analysis, Sayen *et al.* (121) have demonstrated that, after ligation of a major coronary artery in the dog, three zones of oxygen tension in the infarcted area can be identified during inhalation of 100 per cent oxygen. Anatomic changes in the guinea pig myocardium differ depending on whether anoxia is induced by changes in the coronary vessels or in the blood composition (122). Cortisone (123) does not appreciably influence the course of acute myocardial infarc-

tion in dogs. Freis *et al.* (124), using primarily the T1824 dye injection method, have investigated various aspects of the circulation following myocardial infarction in man.

Atherosclerosis.—The problem of coronary atherosclerosis is obviously related to the broader problem of general atherosclerosis. An excellent review of the general subject will be found in a recent symposium (124a) Since coronary artery involvement is being used as a guide to the presence of general atherosclerosis, the experiments of Pick warrant consideration. As reported by Katz (125), he has demonstrated that estrogens, prophylactically administered to chicks, will inhibit coronary atherosclerosis induced by feeding cholesterol, but that aortic atherosclerosis is not prevented; this again emphasizes that atherosclerosis is a patchy process and that involvement of one vessel does not necessarily indicate involvement of the others. Of interest in this respect is a review of anatomic findings in three subjects in whom the right coronary artery arose from the pulmonary artery and the left from the aorta. In each of these subjects, atherosclerosis was present in the systemic coronary but not in the coronary artery arising from the low pressure circuit (126).

In Katz's laboratory, studies continue on the production of atherosclerosis by cholesterol feeding and on the effects of modifying factors (125). Steiner *et al.* (127), from observations made on a group of subjects with coronary disease, conclude that the increase in serum cholesterol-lipid phosphorous ratio permits deposition of cholesterol in the arteries since the amount of lipid phosphorous becomes insufficient to maintain the cholesterol in solution. Gofman *et al.* (128) review their experiments which indicate that atherogenesis is primarily related to derangement of lipid transport rather than any specific lipid. However, Keys (129) can find no evidence which convincingly suggests that the S_f 10–20 lipoproteins are more closely related to atherogenesis than is the concentration of total cholesterol in the serum. He suggests controlling atherosclerosis by limiting total caloric intake and restriction of all fats rather than cholesterol per se. Gertler *et al.* (130) suggest that the uric acid X cholesterol-phospholipid ratio is a more significant index of coronary disease than any of these factors separately. In brief, all authors seem convinced that alterations in lipids or in their transport are involved in atherosclerosis but the intimate mechanism of its production remains to be discovered.

Pulmonary Circulation

Vasomotor control.—The question of vasomotor control of the pulmonary circulation is still unresolved. Daly & Hebb (131) have identified pulmonary vasomotor fibers in the vagus and sympathetic nerves of the dog. They, as do others, use the term "pulmonary vasomotor response" to indicate a change in pulmonary artery pressure upon application of a given stimulus, but recognize that the vessels proper may not be effecting an active response. Pearce & Whitteridge (132) established a direct relationship between pul-

monary artery pulse pressures and activity recorded from the "pulmonary vascular fibers" in the cervical vagus, and presented evidence to the effect that the receptors for these fibers lie on the arterial side of the pulmonary vascular bed. Aviado *et al.* (133), using the perfused heart and pulmonary circulation of the dog, demonstrated baroreceptors in the right atrium and suggest that pressoreceptors and receptors sensitive to veratrine are located on the pulmonary venous side. The effects of experimentally induced anoxia upon pulmonary vascular pressures have been used to demonstrate pulmonary vasomotricity (134 to 140) and chronic anoxia has been indicted as a mechanism for increased pulmonary vascular resistance in disease (141). However, Edwards (142), in his studies on the effects of lung inflation and epinephrine on pulmonary vascular resistance, has pointed out that the simple calculation of resistance as pressure-flow ratio ignores changes in vessel caliber which are passively induced by increased volume flow. The passive changes may conceal or simulate active responses due to external stimuli. Others (143, 144) have reached similar conclusions. Although Stroud & Rahn (145) have shown that the increase in pulmonary vascular resistance which accompanies low oxygen breathing in dogs could be abolished by sympathectomy, their demonstration does not exclude the possibility that nonvascular portions of the lung are contributing to, or determining, the change in calculated resistance. Shunting of blood from an anoxic lung has been demonstraged by direct measurement by Peters & Roos (146) in open-chest dogs. Atwell *et al.* (147), using bronchospirometry in the intact dog, also concluded that anoxia caused shunting of blood away from the anoxic lung, but could not exclude the possible role of local accumulation of carbon dioxide in effecting this shunt.

A valuable contribution to the understanding of the effects of induced anoxia on the pulmonary circulation has been made by Nisell (148). He demonstrated that respiratory gases brought into contact with the pulmonary vascular bed by way of the bronchial tree affected pulmonary vascular resistance differently than did the same gases reaching the lungs via the blood stream. He concluded from his experiments that anoxia and increased carbon dioxide dilate the pulmonary artery and arterioles but constrict the pulmonary veins or venules; the mode of entry of the gas into the lungs, by breathing or pulmonary circulation, apparently determines which vessels are primarily affected. In a subsequent paper (149) he stresses the role of extravascular smooth smucle in changing pulmonary vascular resistance. Thus, the changes induced by the elastic forces developed in the lung per unit tidal air volume may be in the opposite direction to the forces acting to directly stimulate the vessel wall. According to his concept, anoxia tends to constrict pulmonary venules by direct action on their wall, but to dilate them by virtue of its effects in decreasing lung elastance. Nisell further emphasizes that small pulmonary vessels are contiguous with structures, the elastic properties of which may influence resistance to blood flow. It is apparent that pathologic alterations in the enveloping lung parenchyma, as

well as physiologic variations in the diameters of adjacent bronchioles, may significantly contribute to the *in vivo* distensibility curve of the small pulmonary vessels. These extravascular factors in the rather unique parenchyma of the lungs warrant more consideration than has heretofore been afforded them in evaluating and interpreting changes in pulmonary vascular resistance.

Bean *et al.* (150) have confirmed in the isolated perfused dog lung that carbon dioxide constricts pulmonary venules and bronchioles, and have concluded that active or passive pooling of blood in the pulmonary arterial bed may result. In addition to the direct action of carbon dioxide, a local anticholinesterase action is suggested. Nelemans (151), from experiments with the rat heart-lung preparation, has indicated that coronary venous blood contains a labile substance which acts to dilate the pulmonary vascular bed.

The effects of epinephrine on the pulmonary circulation have been investigated in the isolated cat lung (149), under carefully regulated conditions in the isolated lung-lobe (142), and in intact man (152). Besides pressure alterations, which are variously interpreted, attention may be called to the release of leukocytes and platelets following intravenously administered epinephrine (153).

Smith & Coxe (154) have investigated the actions of various drugs on the larger isolated pulmonary vessels, and Binet & Burstein (155) have described a pulmonary hypertensive effect of small volumes of hypertonic saline administered intravenously.

The effects on the pulmonary circulation of chronic pulmonary disease are described by Harvey *et al.* (141) and Mounsey *et al.* (156). A mechanism for left ventricular strain related to the development of collateral bronchial circulation in chronic pulmonary disease has also been suggested (157).

Pulmonary capillary pressure.—Because of the hazards and technical difficulties associated with direct pressure recording from the left side of the heart in man, an indirect method of recording pressures through a catheter wedged in a pulmonary artery branch has been much employed in recent years. The effects of wedging and cessation of flow on vessel caliber and wall-tension distal to the obstruction are not known. Although it is now recognized that the pressure so recorded ("PC" pressure) is not mean pulmonary capillary pressure (158), the problem remains to decide, particularly in subjects with pathologic alterations of the vessel wall, exactly what pressure is being recorded through the poor manometric system composed of catheter and obstructed vessel.[3] Attempts to define this measurement continue. Weissel *et al.* (158) recorded pulse contours from pulmonary veins obstructed by a catheter passed through an interatrial septal defect and observed that the mean pressures so recorded exceeded simultaneous pressures in non-obstructed pulmonary veins and atria. They could not relate contours ob-

[3] See also the animated discussion of "PC" pressures by Burton in the chapter on Peripheral Circulation in this volume. Ed.

tained from the obstructed vessels to simultaneous pressure pulses from the pulmonary artery, and did not exclude a possible contribution from the bronchial arteries. Although previous studies reported by Lagerlof & Werkö in 1949 indicated that "PC" pressure, as usually recorded, reflects pulmonary venous events and that characteristic contours may be identified in the presence of a mitral valve which is stenosed, leaking, or both, Calazel *et al.* (159) failed to find evidence of a venous pressure pulse in their "PC" tracings.

The experimental studies of Ankeney (160) go far in solving some of the problems intrinsic to this ingenious technique. In normal dogs, "PC" tracings devoid of oscillations consistently exceeded left atrial pressure by a few mm. Hg, and reflected changes in direction of pressures in the left atrium but not in the pulmonary artery. It was also possible to reproduce experimentally the oscillating pressure tracings ascribed to organic mitral disease in man; however, these undulating curves in dogs apparently did not reflect left atrial pressure changes related to mechanical events, but instead resembled pulmonary artery pressure pulses. Ankeney concludes that "PC" tracings are only reliable indices of left atrial pressures when devoid of oscillations. He also presents evidence which indicates that the ability to withdraw highly oxygenated blood through the wedged catheter does not necessarily indicate that pulmonary capillary or venous pressures are being selectively recorded. These observations are obviously of interest to those who have made an extensive use of "PC" pressures as an index of left atrial events and pressures in man. Whether these results in normal dogs can be extrapolated to those obtained in human subjects with mitral disease remains to be established, especially since the physical characteristics of the pulmonary vascular bed may be modified by congestion, as well as intrinsic or parenchymatous alterations.

Pulmonary infarction has been reported to follow wedging of the distal pulmonary artery by a catheter in patients with mitral disease (161). This complication was minimized in Dexter's laboratory by substituting autoclaving for chemical sterilization. It is not clear why this complication, if from chemical agents, should have been confined solely to patients with mitral stenosis. The duration of obstruction to flow would appear as a probable factor favoring infarction in these patients with congested lungs.

Pulmonary intrathoracic blood volume.—Attempts continue to measure and fractionate the volume of the intrathoracic segment of the circulation. Everett (162) has used an isotope dilution technique to determine the blood volume changes in the guinea pig lung immediately after birth. Sjöstrand (163) has employed pulmonary volume measurements to determine changes in intrathoracic blood volume in man, and concludes that the vascular bed of the pulmonary circulation acts as a blood reservoir and stabilization chamber for the left ventricle. The heart volume, a variable fraction of intrathoracic volume, is still estimated from radiologic measurements (164), and modifications of the methods of Rohrer & Kahlstorff have been applied to the problems of cardiac dilatation and hypertrophy (165). Nylin (166) has

reviewed his experiences with radioactive phosphorous in determining the residual heart volume. Bing *et al.* (167) have used cardiac catheterization and injection of T1824 dye through a specially designed catheter to determine the residual volume of the right ventricle, and discuss some of the factors which limit this type of measurement. Since most current investigations of this problem are using a modification of the dye-concentration curve method of Stewart-Hamilton to estimate the volume of blood contained between the sites of injection and sampling, the mathematical analysis of factors influencing the circulation time by Pearce *et al.* (168) warrants consideration. Attention has also been called to the fact that since the blood volume measured following a dye injection into the pulmonary artery includes left atrium, left ventricle, pulmonary capillaries and veins, and systemic arteries, changes in one area may mask reciprocal changes in another (169). Furthermore, in the presence of an abnormal circulation, recorded curves are often poor, mixing potentially incomplete, and stagnant depots of blood may fail to participate (170). Consequently, caution is indicated in the interpretation of results by this method. A mathematical analysis of various factors influencing the time-concentration curve in artificial flow systems composed of a series of bottles of different volumes into which dye is injected, has been presented by Newman *et al.* (171). A comparison is drawn between the intrathoracic blood volume and a three chambered model flow system with the largest volume in the middle chamber. Tompkins *et al.* (172) found that circulating "central blood volume" (cardiac output multiplied by mean circulation time) and Newman's "lung blood volume" (171) were both apparently higher in normals than in subjects with mitral disease.

Influence of respiration.—Various aspects of the influence of respiration on the right heart and pulmonary circulation have been investigated in the dog (173), in the cat (143) and in the isolated dog lobe (142, 144); its effects on the left heart and systemic circulation have been described in the dog (174). The influence of Cheyne-Stokes respiration upon the pulmonary circulation have been studied in man (175). Pulmonary arterial pressures have been recorded during induced cardiac arrest in two subjects (176).

Miscellaneous.—Harrison (177) produced experimental pulmonary hypertension in rabbits by continued intravenous injections of minute fibrin clots. Gamble & Patton (178) caused pulmonary edema by hypothalamic lesions, using a stereotaxic instrument in rats. Carlson *et al.* (179) produced pulmonary artery systolic hypertension in dogs by progressive removal of lung tissue at successive operations. Peirce (180) has described a method for the experimental production of pulmonary arteriovenous fistulae in dogs. Takaro *et al.* (181) have recorded the pulmonary and systemic changes following the establishment of acute and chronic arteriovenous pulmonary fistulae in dogs.

Electrocardiography

Two volumes published in other countries merit particular consideration: Sodi-Pollares (182) has presented in Spanish an admirable introduction to

and review of current concepts; Schaefer's book (183) in German is an excellent reference source for continental European ECG[2] literature, particularly oriented with regard to vector analysis.

It is manifestly impossible to review here the multitude of papers on ECG which appeared during the last year. Hence we shall limit our survey to some of those papers which are of unusual experimental interest or appear to have theoretical implications.

Physiology.—Butterworth & Thorpe (184) have adduced experimental support for the theoretical considerations of the body as a homogeneous volume conductor and application of Einthoven's postulates. Mauro *et al.* (185), in an extension of previous observations in man, have recorded the equipotential lines of the electric field of the dog heart as it exists on the body surface. They indicate that the observed geometric pattern does not resemble that of a surface doublet, and suggest that the theoretical concepts of ECG which are based thereon may need re-evaluation.

Methods.—Attempts to record potentials from relatively inaccessible surfaces of the heart continue. A bronchial lead has been used (186) and esophageal leads have been simplified (187) and used to explore left ventricular cavity potentials in man (188). However, anatomic relations between esophagus and adjacent structures may vary (189) and complicate the interpretation of this indirect type of recording. The esophageal lead may (190) or may not (191, 192, 193) supplement information available from more standard leads in the presence of posterior myocardial infarction.

Bundle branch block.—Mechanical and chemical block or both, of the bundle branches have been produced by Aranjo & Aquilar (194) and Frau (195). Their results do not support the concept recently propounded by Segers (196) that the delay in transmission in bundle branch block is localized in the Purkinje-myocardial synapses. In another report, Segers (197) has presented an exhaustive review of transitory intraventricular blocks manifested by ECG contours which are morphologically identical with permanent blocks. A normal QRS associated with a premature beat during intraventricular block is ascribed to a super-normal phase of recovery of the intraventricular conduction system. Alzamora *et al.* (198, 199, 200) review the course of ventricular excitation in normal subjects and in subjects with conduction disturbances.

Arrhythmias.—Prinzmetal and co-workers have summarized in a book (201) and in a review article (202) their unitarian concept as to the nature of the atrial arrhythmias which is based on cinematographic, ECG, and oscillographic observations on dog and man. The four atrial arrhythmias (premature systoles, paroxysmal tachycardia, flutter, and fibrillation) are pictured as having a common mode of origin, i.e., emission of stimuli from an ectopic focus in the atrium. This concept is supported by Simonson & Berman (203) on the basis of their analysis of flutter and paroxysmal atrial tachycardia with block.

The mechanism of paroxysmal nodal tachycardia with retrograde heart block (204), and the role of anesthesia (205, 206), sympathetic nerve stimu-

lation (207), and temperature (208) in producing ventricular fibrillation have been evaluated. Van Bogaert *et al.* (209) have contributed a detailed analysis of experimentally produced premature contractions in dogs. Parasystole was induced by Scherf & Chick (210) in the dog by topical application of veratrine and veratridine, eliciting simple interference between sinus and ectopic rhythm. The nature of "protection block" in parasystole is discussed.

A-V conduction and WPW syndrome.—Ehrentheil *et al.* (211) describe an inverse relation between P-R and R-R interval in sinus arrhythmia. Scherf & Dix (212) have observed a shortening of the atrioventricular conduction time in 26 of 31 patients with atrioventricular conduction disturbances when they assumed the upright position. Segers (213) records an instance of alternans of atrioventricular conduction and Benedict & Evans (214) demonstrate in a young adult the production of atrioventricular block with Wenckebach periods by emotional stimulation. Lown and co-workers (215) separate a syndrome of short P-R (0.12 sec. or less) with a normal QRS from the WPW[3] syndrome.

Segers (216) questions whether the WPW syndrome is related to conduction tissue. He extends his previous studies on the synchronization of independent turtle hearts which were in mechanical contact and suggests that certain WPW syndromes may result from a distant synchronizing interaction between atrial and ventricular pacemakers, independent of anatomic connection between the two chambers. His concept is supported by Doumer *et al.* (217) who analyzed the ECG records from two subjects with paroxysmal supraventricular tachycardia, one of whom subsequently developed typical WPW syndrome. Osborne *et al.* (218) and Prinzmetal *et al.* (219) present evidence to indicate that the WPW syndrome is caused by failure of the cardiac impulse to undergo normal delay in the atrial portion of the atrioventricular node, thus producing premature excitation of a ventricular focus.

Q-T interval.—Factors which influence Bazett's K ($Q\text{-}T = K\sqrt{\text{cycle}}$) have been investigated in a variety of species by Robb (220), Geller *et al.* (221), and Siebens *et al.* (222) under various experimental conditions.

Abnormal patterns.—Pruitt and co-workers (223) have demonstrated that the ECG consequences of subendocardial injury depend on the spatial orientation of the traumatized tissue with respect to the exploring electrode. Many papers have been published concerning the genesis of patterns associated with right ventricular hypertrophy. The qR pattern has been investigated by precordial (224) and intracavity leads (225, 226). The effects of cardiac rotation and position are illustrated in three subjects with right ventricular hypertrophy and left axis deviation who were studied by intrapulmonary artery potentials (227).

The effects of drugs on the ECG[2] are included in the general discussion of Drugs.

Vectorcardiography.—A considerable difference of opinion exists as to the

[3] Wolff-Parkinson-White syndrome.

most useful reference system for VCG[2] (228 to 231) and at least four systems are currently in use. Grishman & Scherlis have modified the method of Duchosal & Sulzer and have published an interesting monograph (232) which summarizes their previous reports and describes the fundamental concepts and the application of the cube reference system to normal subjects and patients with heart disease. Grant & Estes (233) have also presented an instructive, albeit limited, approach to the VCG and its relations to the more conventional ECG. Reference has previously been made to Schaefer's book (183). Duchosal & Grosgurin (230) have discussed some of the underlying bases of VCG with special regard to the cardiac center of electrical activity. Burchell *et al.* (234) obtained evidence from the isolated perfused ventricular septum which demonstrated early excitation of the apex relative to the base of the septum. Brumlik & Kossmann (235) have followed changes in the VCG produced by acute reduction of arterial pressure in normal and hypertensive subjects. Abildskov and co-workers (231) used the equilateral tetrahedron to determine the spatial vector in right bundle branch block. The limitations of the various reference systems are indicated in several recent publications (236 to 238).

Electrokymography

Several recent reviews are available (239, 240, 241). Morgan & Sturm (242) have developed a quantitative electrokymograph. Attempts continue to determine stroke volume by EKY[2] (243), and Salans *et al.* (244) have correlated EKY and densograms from the great vessels with intraaortic pressure curves. Ventricular EKY patterns in constrictive pericarditis (245) and pulmonary artery patterns in pulmonary stenosis (246, 247) have been described.

Heart Sounds

Luisada *et al.* (248), using phonocardiography in animals and man, have studied the muscular and valvular factors which contribute to the first sound. Ravin & Bershof (249) conclude from records obtained in subjects with atrial fibrillation, that the most important factor contributing to the intensity of the first heart sound is the position of the mitral valve leaflets at the moment of ventricular systole. Calo (250) analyzes the three groups of vibrations seen with each atrial contraction in a subject with complete heart block, and describes a "fifth" heart sound, which appears after the third sound (251). Sloan & Wishart (252) suggest from experiments with normal young students that the third heart sound is specifically related to the rate of venous return. Rappaport & Sprague (253, 254) continue their studies on deficiencies in stethoscopic apparatus. Rodbard (255) uses models to illustrate pressure-velocity relationships in the production of murmurs.

Ballistocardiography

The ballistocardiograph is being further explored for its value as a guide to clinical problems. Its clinical applications have been recently reviewed by

Dock *et al.* (256). It is still widely used for measuring cardiac output under a variety of experimental conditions (257 to 261). This use is probably unwarranted. Some of the factors which contribute to the contour of the BCG[2] have been investigated: these include alteration in intracardiac flow caused by acute mitral insufficiency (262) and changes in length and position of the aortic arch during systole (263). Of particular interest are the observations of Starr & Hildreth (264) on the effects of aging on the ballistocardiogram contour, which they ascribe to a slower lifting of its load by the heart.

Biochemical Alterations and Drugs

Anoxia.—Gelfan & Werner (265) have extended their studies of the cardiovascular responses following explosive decompression of monkeys to extreme altitudes, a method for induction of abrupt anoxic anoxia. Whitehorn & Bean (266), using decerebrate dogs, obtained responses to oxygen at high pressure (60 pounds) which were similar to those with low oxygen and high carbon dioxide at ambient pressures. The early effects including bradycardia and slowed atrioventricular conduction, were shown to be dependent upon the integrity of the vagi, but prolonged effects were independent of vagotomy and stellatectomy. Binet *et al.* (267) have demonstrated, in dogs breathing pure nitrogen, a fixed order of suppression of cardiac activity which terminates in cardiac arrest. By varying experimental conditions during anoxia, bradycardia (268) or ventricular tachycardia (269) could be produced.

Electrolytes.—A general review of the effects of various electrolytes on the ECG has been presented by Merrill (270). Investigators primarily interested in the effects of hypo- or hyperpotassemia should consult the excellent review of Sheppard (271) on recent developments in potassium and cell physiology. Anatomic changes due to hypokalemia are described by Keye (272). Butcher *et al.* (273) were able, by varying the concentration of other cations in the perfusate, to reproduce in the isolated dog heart the ECG changes which have been observed in man during hypokalemia (274). The disturbances of cardiac mechanism incident to hyperkalemia in man are well described by Levine *et al.* (275, 276) who used the artificial kidney to vary serum levels. Lamelas & Asorey (277) have described the ECG changes following the administration of a single dose of potassium salt by mouth to a large series of human subjects. Del Castillo-Nicolau *et al.* (278) have indicated the depressant effect of increased potassium on the frog heart. Roberts (279) has used cortisone to effect reversion of ECG changes in adrenalin-insufficient, hyperpotassemic dogs, and observed that the changes in ECG are parallel to changes in serum potassium and sodium. Cohen & Braun (280) and Oker (281) have described ECG changes associated with uremia: the latter did not observe parallel changes in ECG and serum potassium level. Attention is again called to the antagonism between potassium and digitalis (281). Cardiac muscle mass in rats has been shown to be reduced by excess dietary potassium (282).

Digitalis glycosides.—Loubatières (283) has presented an excellent, general review of the methods used to study these drugs and of their pharmacology. The mode of action of digitalis compounds on the hearts of various species has been investigated by Sjoerdsma & Fischer (284) using radioactive digitoxin. They conclude that a large fraction of the digitoxin present in the heart muscle is in the form of metabolites which are more firmly fixed to the heart than the parent substance. With Johnson (285) they extended their observations to the tissue distribution and excretion of digitoxin in normal digitoxin-sensitive cats, in normal digitoxin-insensitive rats, and in rats with heart failure. Their conclusions are similar to those obtained by Bine and co-workers in the normal rat (286) which indicate that this animal has little or no ability to metabolize digitoxin or retain its derivatives, except in the presence of heart failure. The cat, on the other hand, retains the parent drug and its metabolites in the heart; its kidney is apparently capable of excreting preferentially the water soluble metabolites and of retaining the unchanged drug for more gradual excretion. Hilton (287) reports that extracts of heart and liver have the ability to break down digitoxin to form digitoxigenin. Bine *et al.* (286), using the embryonic duck method, conclude that the cardiac action of digitoxin is not due to the avidity of cardiac tissue for the drug, but rather to a qualitative property of the drug to which the myocardium responds. Levine *et al.* (288) review evidence that the digitalis pattern on ECG is due to alteration of repolarization in the apical region of the heart. Magnesium sulfate has been found useful in controlling ventricular arrhythmias induced by digitalis (289). Moe & Mendez (290) could demonstrate no significant difference in the effects of several cardiac glycosides on conduction velocity and ventricular excitability in the dog's heart.

Harvey *et al.* (291) have studied the action of digoxin on enlarged hearts without failure and have elicited a response similar to that observed in normals. Eichna *et al.* (292) observed a prompt improvement in cardiodynamics following the administration of digoxin intravenously to subjects in heart failure, a rapid marked water and electrolyte diuresis, and a slower inconsistent improvement in renal hemodynamics. The mechanism of digitalis diuresis has been investigated by Farber *et al.* (293).

Quinidine, procaine, procaine amide.—Harris *et al.* (294), using their standard method for producing ventricular tachycardia following myocardial infarction, effectively controlled the arrhythmias in 50 to 60 per cent of the animals by intravenous quinidine lactate or gluconate. Toxic manifestations were produced in many, but could be minimized by concomitant administration of morphine sulfate. The quinidine-like action of procaine, because of its hydrolysis product, diethylaminoethanol, was too brief and attended by too many toxic reactions to be of practical value (295). On the other hand, they agree with others who have used different methods of inducing arrhythmias (296, 297) that procaine amide, an analog of diethylaminoethanol, is particularly effective in controlling arrhythmias of ventricular origin. Wedd *et*

al. (298) demonstrated that procaine amide elevated the threshold for electrical stimulation of the turtle heart and prolonged the conduction time in the ventricle but, in contrast to quinidine, did not depress contractility. Toxic reactions have been encountered in animal experiments (295, 297) which may in part be related to the route of administration and the experimental preparation used for study. Results of experiments in man generally indicate that procaine amide is more effective in interrupting ventricular than atrial arrhythmias (299, 300). When the latter are of recent origin, they appear to be more susceptible to procaine amide than chronic arrhythmias (301, 302) but toxic manifestations are common when doses adequate to control the auricular arrhythmia are administered.

Miscellaneous drugs.—Effects of mercurial diuretics on the heart have been reported (303). In addition, results of studies have appeared on their elimination from the plasma (304) and body (305), and their mode of action on the kidney (306). The comparative effects of epinephrine and norepinephrine on the myocardium have been described (307, 308). Cortisone has been reported to synergistically affect the positive inotropic and chronotropic actions of epinephrine (309) and to cause ECG changes independent of serum potassium level (310). The ECG effects of barbiturates in man have been evaluated (311) and the antifibrillatory properties of the lesser alkaloids of opium explored in animals (312).

PHYSIOPATHOLOGY OF CARDIAC DISEASE

Congestive Heart Failure

Two excellent reviews have been published (313, 314). The first considers the hemodynamic aspects of congestive heart failure and the other stresses the role of abnormal fluid distribution. Cournand, Lequime & Regniers (315) have reviewed modern techniques of studying hemodynamics in man, and compared results in normal man, compensated heart disease, and various types of cardiac failure. An extensive bibliography, including references up to June 1951, is presented at the end of each chapter.

Animal experiments.—Various experimental procedures designed to reproduce the syndrome of clinical congestive heart failure have been investigated. Cannon (316) has produced the congestive state in rats, using low-protein followed by low-potassium diets. In dogs, a similar state has been produced by combining arteriovenous fistulae with salt feeding (317), or imposing acutely a cardiac load in a previously damaged heart (318). Barger *et al.* (319), using graded exercise, contrast the fixation of cardiac output in dogs with combined tricuspid insufficiency and pulmonary stenosis with its increase in normal dogs and dogs with isolated tricuspid insufficiency.

Attempts continue to define the respective roles of elevated venous pressure and decreased cardiac output in initiating the congestive state. Fishman *et al.* have previously described the marked sodium retention associated with generalized elevation of systemic venous pressure induced by

an inflammatory pericardial effusion in dogs. Stamler *et al.* (320) were able to reproduce these findings by ligating the inferior vena cava above the liver. Frieden *et al.* (321), extending these studies in the same laboratory, have more recently demonstrated that sodium retention need not be related to elevation of venous pressure in any specific bed, but that engorgement of any peripheral bed of adequate size will initiate sodium retention without change in cardiac output or glomerular filtration rate. These reports are pertinent to the results obtained in humans by Farber *et al.* (322), who used an inflated balloon to locally elevate pressure above and below the renal veins. Regardless of the position of the balloon, similar effects on sodium and water excretion were generally observed. Attempts to relate decreased cardiac output to sodium retention in dogs by Levy & Berne (323) are complicated by concomitant reductions in glomerular filtration rate, other hemodynamic changes, and increasing serum sodium concentrations.

Human studies.—The significance of repeated observations in patients with various types of heart disease prior to, as well as in the state of cardiac failure has been stressed (315). Factors contributing to the elevation of venous pressure are considered in several papers. Brown *et al.* (324) and Albert & Eichna (325) have studied the effects of exercise in patients with heart failure. Fejfar & Brod (326) stress the role of the sympathoadrenal system in initiating arteriolar vasoconstriction and increase in venous tone. Halmagyi *et al.* (327) have used sleep and various blocking agents to evaluate the neurogenic and muscular contributions to the high venous pressure of heart failure. A consistent reduction of about 35 per cent was obtained by these methods, and the authors conclude that mechanical factors account for the remaining 65 per cent. Duomarco *et al.* (328), who used angiocardiography, failed to demonstrate in subjects with heart failure who assumed the upright position the intrathoracic venous collapse regularly observed in normal subjects. Prentice *et al.* (329) review the literature regarding blood volume in congestive heart failure. Using labelled red blood cells (P^{32}) and venous hematocrits, they could demonstrate no significant increase in blood volume in 18 of 28 subjects in frank heart failure. This paper is probably a forerunner of a large series of technical and conceptual argumentations. Gauer *et al.* (330) believe that stretch receptors in the pulmonary vessels, great veins, and heart contribute to the control of the blood volume.

The role of the kidney and fluid distribution.—Friedberg (331) and Rosenheim (332) review exhaustively some aspects of this subject as they pertain to heart failure. The steps which relate cardiac disability to altered kidney function and fluid distribution remain to be defined. Redistribution of fluid (333, 334), changes in its composition, antidiuretic hormone activity (334, 335), increased renal venous pressure (321) all, under certain conditions, seem to influence the renal handling of fluid and electrolytes. Elkinton & Squires (314) implicate a primary alteration in cellular metabolism, possibly mediated by anoxia, as responsible for alterations in fluid distribution in the congestive state. Some of the limitations of available methods for determi-

nation of the distribution of body fluids have been discussed (336, 337, 338).

In clinical studies, it is often difficult to dissociate the changes in electrolyte composition due to the heart failure *per se*, and those due to treatment. In the untreated edematous cardiac patient, Stock *et al.* (339) describe normal serum sodium concentrations. In cardiac patients who have been treated with mercurial diuretics, hyponatremia, hypochloremia, and metabolic alkalosis are frequent (340). Miller (341) has attempted to trace the changes in volume and electrolyte composition of patients recovering from heart failure.

Ray & Burch (342) review the physiologic bases and clinical uses of mercurial diuretics. Lesser *et al.* (343) indicate that mercurial diuretics in edematous individuals causes an isotonic diuresis, high in chloride and variable in amount of sodium and potassium. The effects of mercurial diuresis on intracellular composition are discussed (343, 344). Schroeder (345) contrasts the effects of mercurial and other diuretics in heart failure. Lowe (346) has investigated mechanisms controlling water loss in patients with heart failure during recovery. Sleisenger & Freedberg (347) illustrate the hazard of ammonium chloride acidosis in the presence of intrinsic renal disease. Friedberg & Halpern (348) have used carbonic anhydrase inhibitor 6063 to reduce tubular reabsorption of sodium.

Hormonal factors.—Reynolds (349), using sweat sodium concentrations, could find no evidence of increased adrenal cortical hormone activity to account for the sodium retention of congestive heart failure. Total neutral lipid-soluble steroids excreted in urine per 24 hr. are also normal (350). Berger & Steele (351) demonstrated, by means of cation-exchange resins, that the colon of the edematous patient retains sodium to a greater than normal level and conclude that this effect is part of a general suppression phenomenon including kidney, sweat, and salivary glands. Sherer & Greer (352) call attention to subjects with cyclic premenstrual congestive heart failure, and Albert & Smith (353) were able to cause the clinical and hemodynamic manifestations of heart failure by administration of ACTH, cortisone, or desoxycorticosterone. Goldman (354) has suggested that the liver may be humorally related to the reversal of the normal diurnal cycle of salt and water excretion in heart failure, and anoxic centrolobular necrosis of the liver (355) has been postulated as a mechanism by which normal inactivation of antidiuretic substances is abolished leading to primary water retention. It is apparent that although significant advances are being made in understanding the hormonal contribution to congestive heart failure, the final answer is not yet available.

A series of six experimental and clinical reports on the use of cation exchange resins to promote negative sodium balance has appeared (355A). Other studies attest to current interest in this method (356 to 360).

Miscellaneous therapy.—In addition to the use of digitalis, diuretics, and cation-exchange resins as specific forms of therapy, Cossio (361) and Donzelot *et al.* (362) have recorded their experiences with the use of ligation of

the inferior vena cava below the renal veins for management of intractable heart failure. Ellis *et al.* (363) use the results of hemodynamic studies to question the advantages accrued to the circulation by induction of therapeutic myxedema, whereas Blumgart *et al.* (364) present a somewhat more optimistic clinical report.

Mitral Stenosis

The stimulus of therapeutic cardiac surgery, improved recording apparatus, and right heart catheterization has intensified the application of physiologic methods to the altered circulation produced by mitral stenosis in man (365). The chronic hemodynamic changes have heretofore been poorly reproduced in the laboratory. Recently, Ellison and co-workers have succeeded in producing mitral stenosis in the dog by circumferential ligature of the mitral valve (366). However, at the present time, the large body of pathophysiologic data is derived from post mortem observations supplemented by physiologic measurements made prior to, during, and following intracardiac surgery in man.

The fundamental hemodynamic alterations resulting from chronic mitral stenosis in man seem well established (101, 169, 315, 367 to 371). In mild mitral stenosis (Grade 1 and 2, classification of the New York Heart Association), right heart, pulmonary and, systemic pressures and flows are usually within normal limits; exercise may elicit pulmonary hypertension. In severe symptomatic mitral stenosis, without heart failure, the cardiac output at rest tends to be reduced and blood pressures are usually increased throughout the pulmonary vascular tree; with exercise, the cardiac output rises little, if at all (372), and the pulmonary blood pressures tend to increase. The onset of heart failure (315, 372) is indicated by an elevation of the end-diastolic pressure in the right ventricle. Pulmonary congestion and a prolonged circulation time reflect obstruction at the mitral valve rather than heart failure. The advent of atrial fibrillation in mitral stenosis is associated with a decrease in cardiac output (373, 374).

Pressures measured after wedging a catheter in a pulmonary artery have been used in mitral stenosis as indices of pressures in the less accessible left atrium-pulmonary vein system. The validity of this measurement is discussed above. Evidence has been presented (169, 371, 372) that the pressure recorded through this obstructing arterial catheter is elevated in mitral stenosis. However, caution must be exercised in quantitatively relating this pressure to pressures and events in the left atrium. It is not established whether a peak of abnormal amplitude in the curve recorded during early diastole is due to mitral insufficiency or transmission of the arterial pulse wave. If this peak is an artefact related to transmitted waves from the pulmonary artery, the recorded pressure will exceed actual left atrial pressures. This becomes a significant limitation to the use of mean "PC" pressure to calculate pulmonary arteriolar resistance and to estimate cross-section area of the mitral valve (370, 371). The latter estimation is based on engineering

hydraulic formulae originally devised for the calculation of the size of a fixed, smooth, circular orifice in a rigid constant flow system. Whether it is valid to extend these formulae to the calculation of the cross-section area of a mitral valve orifice, variably distorted and housed in an elastic pulsatile system, is a matter for debate. The limitations of this application recognized by Gorlin *et al.* (375) have been emphasized by Eliasch (101).

Anatomic alterations in the pulmonary vascular bed contribute to the hemodynamic picture. These anatomic changes cannot be quantitatively predicted from the clinical degree of mitral stenosis (376), but the more severe the stenosis and the longer its duration, the greater the likelihood of pulmonary vascular pathology. The changes in the smaller pulmonary arteries and arterioles may constitute an obstacle to the output of the right ventricle. It has even been claimed that increased resistance in the pulmonary arterial system constitutes a homeostatic mechanism which protects the pulmonary capillary bed against surges of pressure which might precipitate pulmonary edema (370). Gorlin *et al.* (169) could consistently relate clinical pulmonary edema to "PC" pressures greater than plasma oncotic pressure. On the basis of experiments using exercise, they concluded that an acute increase in cardiac output was largely responsible for the increased "PC" pressure observed in these patients. However, Eliasch *et al.* (372) question their use of the Fick principle to calculate cardiac output during the brief imposition of an acute work load on physically-limited subjects.

The plasma volume is increased early in the course of mitral stenosis (101). Werkö *et al.* (377) have demonstrated that even in the absence of heart failure blood is being shunted away from the kidney. Goldberg *et al.* (378) have found that whereas normal subjects and subjects with mild mitral stenosis show an overshoot of systemic blood pressure and a tachycardia following the Valsalva maneuver, the severe mitral stenosis group did not.

Data concerning the immediate, early and late hemodynamic effects of surgery are gradually accumulating (101, 315, 368, 379, 380). Munnell & Lam (379) have recorded in the operating room, pressure tracings from the pulmonary artery and left atrium immediately before and after commissurotomy. Gorlin *et al.* (380) describe later changes (two to six weeks following valvulotomy) which include a decrease in pulmonary congestion and in the calculated arteriolar resistance as well as an improvement in right ventricular function without change in cardiac output. However, others (315, 371) have noted that despite clinical improvement, pulmonary vascular pressures may remain elevated immediately after surgery, and only gradually after several months, start reverting toward normal.

Problems relating to mitral insufficiency have received some attention. Thus, in man, it has been observed that mitral insufficiency aggravates further the altered hemodynamics of mitral stenosis (367, 375). In a circulatory model, arterial hypertension has been shown to increase mitral regurgitation (381), and in experimentally induced mitral insufficiency, Lasser & Loewe

(382) have recorded from the esophagus, with some fidelity, transmitted left atrial pressure pulses.

Congenital Malformations

Since it is manifestly impossible to review the large number of clinical papers on this subject which contain physiologic measurements, attention is called to the excellent book edited by Soulié (383), and the series of critical articles which have appeared in volume 12 (1952) of the *American Journal of Medicine.*

Everett & Johnson (384) have studied late-fetal and newborn pups and describe a marked reduction in patent ductus flow 1 to 2 hr. after birth, with the most marked reduction about the ninth hour *post partum.* Anatomic closure is complete at about the eighteenth *post partum* day.

Deuchar & Knebel (385) have attempted to measure the "Windkessel" function as well as the peripheral resistance of the pulmonary cirulation in children with congenital heart disease. The lack of adequate data for normal children is a serious limitation in their application of theoretical considerations. Martin & Essex (386) describe a method for the production of interatrial septal defects, and record pressures after production of the defect. Brecher & Opdyke (387) have demonstrated that, whereas a small interatrial defect was effective in relieving acutely induced right ventricular strain in dogs, a large defect was deleterious, due to change in dynamics of the left as well as the right atrium. In experimental coarctation in dogs. Scott *et al.* (388) present evidence for a renal factor in causing the hypertension.

Pericarditis

Metcalfe *et al.* (389) studied the intravascular pressure changes in acute peridardial tamponade. They noted that, as the intrapericardial pressure is acutely increased by introduction of saline into the pericardial cavity, cardiac output falls and pulmonary and systemic arterial and venous pressures tend to approach the same "static pressure," about 20 mm. Hg. This is similar to the value described several years ago by Starr in subjects after death and more recently by Dowling *et al.* (176). Alpert (390) noted excess oxygen uptake during recovery from acute tamponade.

Davis *et al.* (391) modified the irritative cellophane method of Fishman *et al.* to produce a more chronic form of experimental pericarditis, and conclude that the ascites and edema which resulted are primarily due to altered adrenal cortical function and elevated venous pressure. Isaacs *et al.* (392) used localized plaster casts to selectively constrict various cardiac chambers and call attention to the role of the altered volume-elasticity characteristics of the chambers in initiating a series of comepnsatory mechanisms. Hansen *et al.* (393) and McKusick (394) indicate that the "diastolic dip" in the right ventricular pressure curves in constrictive pericarditis is of hemodynamic significance rather than artefactual. The latter author has deduced from EKY records (395) that the "dip" occurrs during the rapid filling phase and

claims that the protodiastolic heart sound of constrictive pericarditis is produced by rapid ventricular filling, and its abrupt arrest.

Cardiac Surgery

Two current problems of interest in cardiac surgery are the exclusion of segments of the circulation to permit intracardiac manipulation, and the management of cardiac arrest.

Burstein & Binet (396) describe a method for exclusion of the left ventricle and Gerst *et al.* (397) use an isolated donor lung to oxygenate venous blood pumped through it. Cowan (398) describes a physiological perfusion pump successfully used in medium size dogs to short-circuit the heart.

Callaghan & Bigelow (399) describe an electric artificial pacemaker for use in cardiac arrest. Guyton & Satterfield (400) attempted to define optimal conditions for electrical defibrillation of the heart through the unopened chest. They conclude that the important factor is the density of current flow through the heart and advocate the use of very large electrodes to permit relatively low voltage (60 cycle current for 0.1 to 0.2 sec. with electrodes larger than the heart itself). Kay & Blalock (401) describe the use of direct intraventricular injection of calcium chloride for cardiac resuscitation.

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EXCITATION AND CONDUCTION IN THE NERVOUS SYSTEM[1]

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It is appropriate to open this review by recording the death of Sir Charles Scott Sherrington, on March 4, 1952. The great indebtedness of neurophysiology to him and to his students is amply recognized and has been sketched by one who knew him well (63). In his lifetime bibliography (63) the final entry is a recently revised edition of his stimulating book, *Man on his Nature* (162).

The Role of Ions in Conduction of Impulses

We shall first review certain work on nerve and muscle fibers studied individually either by actual dissection or by recording through intracellular microelectrodes. Subsequently we shall discuss experimental efforts to extend the principles thus elucidated to nerve fibers under more natural conditions. Excellent reviews of this subject by Alan Hodgkin (75) and by Keynes (93) have recently appeared. Hodgkin, an expert in this area and a master of the expository art, describes present concepts of the nerve impulse as follows:

> The resting potential is explained by supposing that the cell membrane is moderately permeable to the potassium and chloride ions, but is relatively impermeable to sodium and to the internal anions. Any sodium which leaks into the cell is assumed to be pumped out by a secretory process which must ultimately depend on metabolism. A large but transient increase in the permeability to sodium occurs when the fibre is depolarized by an electrical stimulus or by flow of current from an adjacent region of active nerve. Sodium ions therefore enter the fibre at a high rate, and reverse the potential difference across the cell membrane. They also provide the current for depolarizing adjacent regions of resting nerve. The increase in the permeability to sodium is followed by a similar rise in the permeability to potassium. This accelerates the rate at which these ions leave the fibre and helps to restore the membrane potential to its resting value. The interchange of sodium and potassium provides the immediate source of energy for the propagation of nervous impulses, but it must be reversed by a metabolic process during the period of recovery which follows a burst of electrical activity.

The increase in permeability to sodium during a conducted impulse was first postulated to account for the reversal of membrane potential during the impulse [Hodgkin & Katz (81)]. This reversal was originally observed in giant axons of squid and has subsequently been found in many other excitable

[1] The survey of the literature pertaining to this review covered approximately one year ending in July, 1952. A review which includes part of this period has been written by Grundfest (68).

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tissues, most recently in Purkinje fibers of the mammalian heart (41), in axons of frogs (181) and of *Sepia* (176), and in cell bodies of mammalian motoneurons (14, 15, 182).

The literature of the year covered by the present review is rich in evidence supporting the concepts described by Hodgkin. Keynes & Lewis (95) have extended their ionic concentration measurements to single fibers, using the giant axons of *Sepia* and squid to avoid difficulties inherent in multifiber studies. The measurements were made by "activation analysis." Dried axons were exposed to neutrons in a pile; measured radioactivities of the newly formed atoms gave, with suitable calibration, a quantitative estimate of the concentrations of the elements initially present. Sodium, potassium, phosphorus, and chloride were thus studied. A series of axons prepared for analysis at various times after removal from the animal showed a slow loss of potassium and gain of sodium. The potassium loss was not surprising since the resting membrane potential was considerably lower than the potassium equilibrium potential. This was at least partly attributable to the fact that the potassium concentration in the bathing fluid was less than that in *Sepia* blood plasma. Potassium loss and sodium gain were both accelerated during activity. The resultant movements of ions were more than adequate to account for the changes in charge on the membrane during the action potential, in agreement with the hypothesis outlined by Hodgkin. Potassium exchange has also been studied in crab nerves (160), in isolated *Sepia* axons (176), and in vertebrate muscle (32, 176). Movements of phosphorus (13, 95, 135) and of chloride (95) have been measured in nerve.

The net changes in ionic content of axons are the result of imbalance between the rates of inward and of outward movements. Inward and outward fluxes of sodium and potassium were measured separately by Keynes (94) using radioactive tracers and isolated axons of *Sepia*. At rest the outward flux of potassium exceeded the inward flux and the reverse was true for sodium. Activity accelerated the fluxes of both ions in both directions. At rest the ratio of inward and outward fluxes of potassium was consistent with the assumption that the movements of this ion were governed by the gradients of concentration and of potential. Outward flux of sodium, on the other hand, was much too large compared to the inward flux to be explained on the same basis: this is evidence for the existence of a mechanism for "pumping" sodium outward, as postulated in the theory.

Observations quoted above thus showed that the net movements of ions during conduction of impulses were in the directions postulated in Hodgkin's review. The time course of these movements has been investigated by electrical measurements. Thus Hodgkin & Katz (81) explained numerous effects of altered ionic environment on potentials recorded from squid axons by assuming that sodium ions moved inward during the action potential as a result of a large but very brief increase in permeability to this particular ion. Evidence has since been obtained for a similar increase in sodium permeability during the action potential in other tissues, most recently in muscle fibers of the vertebrate heart (31, 41).

Hodgkin and his colleagues (76, 77, 78, 80) have further studied the time course of the permeability changes in giant axons of the squid by measuring the current which flowed through the membrane when the membrane voltage was suddenly changed and held at a new level. This was done with an electronic circuit called a "voltage clamp." After a brief initial surge into the membrane capacitance, the current was related to movements of ions through the membrane. An increase in membrane voltage caused an inward ionic current, i.e., a current in the direction of the applied voltage. Appropriate decrease in membrane voltage resulted in a current that was inward at first, but reversed within a few milliseconds to become a prolonged outward current. The initial inward phase in this case was of special interest because it was counter to the applied voltage. Alterations in this inward current, produced by modifying the external sodium concentration, indicated that it was due to an increase in permeability to sodium and consequent inward diffusion of this ion. Evidence indicated that the later outward current was largely carried by potassium ions; this has subsequently been verified with radioactive potassium [Hodgkin (4)]. Although the inward sodium and outward potassium currents were partly simultaneous, it was possible by means of reasonable assumptions to calculate the time course of each current separately, and thus to derive the time course of the respective membrane conductances. Sodium conductance was found to be only transiently increased during membrane depolarization, returning to the initial value even if the change in membrane potential was maintained. The potassium conductance increased as the sodium conductance returned towards normal and then remained high as long as the membrane potential was altered. This succession of changes in sodium and potassium conductance was in agreement with that postulated to account for normal propagation of the action potential. Further important conclusions from this work were that the inward movement of sodium ions during activity could be accounted for by the gradients of concentration and of potential and that sodium and potassium ions moved independently of one another. Additional implications were discussed in a later paper (79).

These recent and extensive contributions have greatly strengthened the hypothesis that increased permeability to sodium ions and a consequent inward movement of these ions are important steps in the conduction of nerve impulses, at least in excised, isolated axons of certain invertebrates. This hypothesis is also supported by the recent report that the decrease in membrane resistance of squid axons during a conducted impulse varied directly with the external sodium concentration (69). The importance of sodium for conduction of impulses in other tissues has been indicated by the loss of excitability in sodium-free bathing solutions, found in vertebrate and invertebrate nerve fibers, in frog muscle fibers, and recently in mammalian cardiac fibers (41). There appear to be quantitative differences in this sensitivity between fiber types of a given species (34, 122) and between different points along the length of a given fiber (122).

The effects of sodium deficiency are rapid on most excised tissues. In

excised frog nerves with intact connective tissue sheaths, however, several hours are required for development of block in the absence of sodium. Lorente de Nó (120, 121) and Gallego (64) concluded that this long delay could not be due to slowness in removing sodium and that therefore conduction must be possible without this ion. These conclusions have been questioned by various authors, who contend that the connective tissue sheath is a barrier to the removal of ions (e.g., 75, 144). The effects of reduced sodium are certainly much accelerated by removal of the sheath [recently confirmed (34, 126)]; probably this cannot be attributed to damage to the nerve fibers since many if not all effects of sheath removal are reversed by its replacement (33, 126). These observations and others concerning electrotonic potentials (126, 144), phosphate uptake (135), and certain effects of calcium removal (172) strongly suggest that the sheath hinders the movement of ions. However, difficulties arise in interpreting these experiments. These difficulties are avoided when sodium is removed by perfusing a nerve *in situ* through its natural vascular supply (100, 126). In this way conduction in frog nerve is blocked within a few minutes (100); thus the need for external sodium seems to be established in this, as in other species. Although sodium is normally important in vertebrates it is perhaps not irreplaceable. Conduction, blocked by reduction of sodium, can be restored temporarily by addition of lithium (34, 65), of cocaine (123) and possibly of tetraethyl ammonium chloride (122; see, however, 34), although not of ammonium ions (65). In crustacean muscle, conduction is possible when sodium is replaced by choline (52).

Although it seems reasonably well established that depolarization of many kinds of nerve and muscle fibers during the action potential is the result of inward movement of sodium ions, several steps in this process still need to be explained. For example, how is the increase in permeability achieved? Is acetylcholine involved in this, as proposed by Nachmansohn and his colleagues (3, 70)? Why does the sodium conductance return to the resting value even if the membrane is kept depolarized? This process, presumably important for repolarization during the falling phase of the action potential, has been called "inactivation"; it has been distinguished from another kind of inactivation of sodium conductance which occurs if the resting membrane potential is restored (78).

Just as the external sodium concentration is of greatest importance in determining the potential of the active membrane, so the resting potential of the membrane is determined principally by the external concentration of potassium; this is true in the sense that a given change in molarity of potassium alters the resting potential much more than does the same absolute change in molarity of sodium. The quantitative relationships between potential and external potassium concentration are similar in many tissues (75), including frog muscle, which was recently studied by Sandow & Mandel (153). The depolarization produced by potassium is rapid in most tissues, a

new steady level of potential being reached within a few minutes or even in seconds. An exception is found, however, in excised frog nerves with intact epineural sheaths. There is disagreement as to whether this delay in effect is due to slowness in penetrating the sheath or whether the axons in excised frog nerves differ from other tissues in their sensitivity to potassium. Much of the discussion presented above concerning the sheath in relation to sodium is also relevant here. Sheath removal greatly accelerates the polarization changes in frog nerve produced by potassium and other agents (56). Moreover, block of conduction produced by high potassium, which is slow in excised nerves with intact sheaths, is rapid when the same nerves are perfused *in situ* through their blood vessels (100, 126). This strongly suggests that frog nerve fibers, like other tissues, are actually affected rapidly by potassium changes in their immediate environment.

It is interesting to note that a possible physiological role for a sheath relatively impermeable to potassium has been found in phytophagous insects, where potassium levels in the haemolymph are as high as 70 m*M*. This concentration is much greater than that required to block conduction in vertebrate nerves; moreover, in these insects conduction is blocked by injection under the nerve sheath of concentrations as low as 40 m*M* (85). Thus the sheath may here serve to protect the nerve fibers from the high potassium level in the haemolymph. This situation is of course not comparable to that in vertebrates, where the epineural sheath is penetrated by blood vessels.

"Very little is known about the way in which metabolism maintains the resting potential and the ionic concentration differences associated with it" (75). The importance of metabolism has been reaffirmed by recent observations of potassium loss from rabbit nerves during asphyxia (173), sodium gain as well as potassium loss in frog nerves during asphyxia (158), and similar changes in rat and rabbit muscles during ischemia (61, 62). In addition, potassium reabsorption has been observed during oxidative recovery following asphyxia in crab nerves (158). Anaerobic glycolysis may aid in the maintenance of ionic concentration differences, since both potassium loss and depolarization during anoxia of frog nerves are delayed by glucose and accelerated by iodoacetate [(158), cf., however, effects of iodoacetamide (118)]. The mechanisms by which metabolism accomplishes the ion distributions is obscure (36a, 75, 137, 163, 164). Energy must somehow be used to remove sodium against gradients both of potential and of concentration. Possibly the resting membrane potential is generated by the ejection of positively charged sodium ions, and the potassium ions are then drawn inward by this potential. The observations of Keynes (94), cited above, suggest that no metabolically derived forces act on the potassium ions and that their distribution is therefore a consequence of a potential produced by some other cause. Shanes, on the other hand, has postulated that metabolic energy is directly required for potassium uptake and that the potassium distribution is the cause rather than the effect of the membrane potential (158).

Other Aspects of Excitation and Conduction in Nerve Fibers

Excitation of nerve by electric currents.—Earlier investigations of local responses in spinal roots of cats (148) have been extended by Rosenblueth and Ramos. Negative local responses, several milliseconds in duration, were initiated at the make of a cathodal current and at the break of an anodal current (150). The responses under these two conditions, and also during alternating current excitation (149) were all attributed to the same process, one reason being that they were all similarly affected by a number of experimental variables, including the application of direct current and of cocaine. Local responses in nerves have also been studied by several other authors (38, 155, 165).

Numerous interesting reports by investigators at the Sorbonne concerning effects of carbon dioxide, pH, electrotonus, and other factors on oscillatory properties and threshold of nerve will not be discussed here because they have been thoroughly reviewed by Monnier (4, 134). Lussier & Rushton (130) showed that medullated fibers of frog nerves were excitable only at the nodes. A new mathematical theory of excitation has been based on assumptions concerning chemical reactions and ionic permeabilities in the membrane (92).

Saltatory conduction.—Several investigators have recently attempted to determine whether conduction in myelinated fibers is a continuous process in which the activity successively involves all points along the fiber, or whether conduction is discontinuous (saltatory) in nature. In the latter case the generation of the action current is due to changes in the electromotive force of the membrane only at the nodes of Ranvier [see review by Hodgkin (75)]. There is considerable evidence in favor of saltatory conduction past dried-out regions of isolated axons [(88, 167); recently confirmed by Frankenhaeuser & Schneider (60)], and also in isolated axons immersed in a physiological solution (88). Attempting to extend these investigations under presumably more normal conditions, Laporte (106) found no evidence for saltatory conduction in fibers which were left within excised nerve trunks. These experiments have been criticized, however, because the measurements were not of membrane action current, but of membrane action potential: the form of this potential in saltatory conduction would not be expected to differ greatly from that in continuous conduction (75). Moreover, by measuring membrane current Frankenhaeuser has obtained evidence for saltatory conduction in similar, nonisolated axons of excised nerves (4).

Relevant to the possibility of saltatory conduction within the central nervous system is Bodian's recent confirmation and extension of older observations that nodes of Ranvier are present in central axons (11). He studied axons of goldfish, opossums, and humans. Internodal distances in the central nervous system were comparable to those of anterior root fibers of monkeys and varied in approximately linear relation to axon diameter.

Rushton (152) has been able to account for the observed variations of many properties of myelinated fibers by assuming saltatory conduction,

geometrical similarity of internodes, and constant length of nodal gaps. He suggests that the lack of myelin on fibers smaller than 1 μ in diameter results from natural selection in favor of maximum conduction velocity, since the analysis predicts that myelination would slow the velocity in fibers smaller than this, but increase the velocity in larger fibers.

Conduction velocity.—In frog A fibers Lussier & Rushton (129) found that conduction velocity varied in direct proportion to the space constant, which was different for α, β, and γ fibers. In the ulnar nerve of the human forearm, the conduction velocities of the fastest fibers were about the same in subjects ranging from 5 to 50 years, but were slower in older individuals (175). Total conduction time from spinal cord to the hand increased with growth during childhood (175), in contrast to Hursh's previous observation that conduction times were constant during growth in kittens (86). In giant fibers of earthworms velocity of a second impulse was found to be greater than that of the first impulse at certain intervals (25). In frogs slowing of conduction during repetitive stimulation was similar in central and peripheral parts of nerves; recovery after intense fatigue depended on an intact blood supply (28). Dun (42, 43) confirmed the slowing of conduction as impulses passed through dorsal root ganglia and reported that the refractory period for conduction and the interaction between fibers were greater within these ganglia than in nerve trunks.

After-potentials.—After-potentials in ventral roots of cats were recorded by Lloyd (115). Lundberg found that the amplitude of the positive after-potential relative to the negative after-potential was greater in dorsal than in ventral roots of frogs (128). The extremely slow after-potentials in crab nerves were studied by Shanes (160), who suggested that the after-potentials and the changes in membrane potential associated with anoxia were due to shifts in potassium between the intracellular and extracellular phases of the nerve trunk (158). Effects of veratrine and its constituent alkaloids on after-potentials were analyzed by Shanes (161).

Effects of various chemical agents.—Toman has extensively reviewed the pharmacology of peripheral nerve (169). Many fundamental aspects of the action of anesthetics on nerve and other tissues were presented in a symposium (2) and elsewhere (3, 151). Substances classified as "stabilizers" because they blocked conduction without depolarizing the membrane, were found also to reverse the hyperpolarization produced by carbon dioxide and to delay depolarization during anoxia (159). The effects of potassium (36) and of various drugs (35) on nerve conduction were shown to be a function of the sodium concentration. Rubidium depolarized frog muscle (153), as might be expected from its chemical similarity to potassium; however, certain dissimilarities were reported between the effects of rubidium and potassium on electrotonic potentials in spinal roots of frogs (127). Depolarization by lack of oxygen was strikingly delayed by 2.5 or 5 per cent carbon dioxide (103). The excitant action of reduced calcium on excised frog nerves was greatly accelerated by removal of the epineurium or by treatment with saponin (172).

Neuromuscular Transmission in Skeletal Muscle

Intracellular recording with a microelectrode has been applied by Fatt & Katz in a study of neuromuscular transmission in sartorious muscles of frogs (51). The potential difference across the membrane of a muscle fiber was the same at the end-plate as elsewhere (about 90 mv.) and reversed in sign when the muscle fiber was stimulated by a nerve impulse. However, the reversal was smaller in the end-plate region (about 20 mv.) than elsewhere (about 35 mv.). The muscle spike potential evoked by a nerve impulse, when recorded near the end-plate, was preceded and followed by slower phases of depolarization attributable to the end-plate potential. The latter was further studied by blocking transmission with curare and successively inserting an electrode into the same fiber at various distances from the end-plate. The end-plate potential was thus found to spread and disappear exactly as predicted for a cable with leaky insulation. This indicated that active processes of charge removal were limited to a "brief impulse of transmitter activity" during the earliest phases of the end-plate potential. Electrical constants of the membrane obtained from these observations were in agreement with those determined by passing current through the membrane from a second microelectrode inserted close to the one used for measurement. The total amount of charge removed from the membrane by the transmitter was so great as to suggest that the transmitter opened the end-plate to rapid transfer not only of sodium and potassium, but probably also to transfer of all free anions on either side of the membrane. Thus the transmitter appeared to cause a nonselective increase in membrane permeability. This differed significantly from the selective increase in permeability to sodium ions which is believed to accompany the propagated action potential in other regions of the muscle fiber and in nerve fibers.

Random subthreshold fluctuations in membrane potential were found to occur spontaneously in the end-plate regions of muscles excised from frogs, lizards, and tortoises [Fatt & Katz (53)]. When observed with intracellular microelectrodes, each fluctuation had the same form as the end-plate potential evoked by a nerve impulse, but the amplitude was very much smaller (average, about 1 per cent of the normal end-plate potential). Each of these miniature end-plate potentials was assumed to be due to "spontaneous momentary release of many molecules of acetylcholine from a small area of the motor nerve ending." This accounted for their reduction in size by curarine or by sodium-lack, their increase and prolongation by neostigmine (Prostigmine), and their elimination by denervation and by anesthetics. Average frequency varied with temperature and with osmotic pressure. With reduction of calcium, the end-plate potential caused by a nerve impulse was reduced, sometimes to a size no larger than that of one of the spontaneous potentials; the size of the end-plate responses to successive nerve impulses then varied in step-like or "quantal" fashion. It is suggested by the authors that the terminal region of a motor axon has at each end-plate about 100 discrete patches, each of which occasionally releases acetylcholine spontaneously in an amount too small to initiate a propagated impulse. A nerve im-

pulse may serve to synchronize the release from a number of patches and in this way evoke a summated end-plate potential which is normally large enough to initiate a propagated muscle impulse.

The magnitude of the end-plate potential in excised curarized frog muscles was found to vary approximately linearly with the logarithm of the calcium concentration from about 0.5 to 7 mM (37). There were no changes in rate of decay of the end-plate potential elicited by a nerve impulse or in the amount of depolarization of the end-plate region caused by acetylcholine. It was concluded that calcium concentration regulated the amount of acetylcholine released by a nerve impulse.

Blocking and deblocking agents.—The mechanism by which decamethonium (C_{10}) blocks neuromuscular transmission has been analyzed by Burns & Paton (27, 138). By means of an ingenious procedure for rapidly scanning the membrane potential at various points along the gracilis muscle of the cat, C_{10} was found to cause a depolarization, thereby resembling acetylcholine and contrasting with *d*-tubocurarine. The depolarization by C_{10} was restricted to the end-plate region and blocked conduction along the muscle fiber past the end-plate. Localized reduction of electrical excitability near the end-plate was also caused by C_{10} but not by *d*-tubocurarine. It was concluded that localized depolarization accounted for all the observed effects of C_{10}, especially since these effects were abolished when the polarization was restored by applied currents or by *d*-tubocurarine. Observations of other investigators, however, indicate that C_{10} has additional actions not restricted to the end-plate regions, at least in certain species (89).

The concentration of curare required to block myoneural junctions in excised rat diaphragm preparations was found to vary greatly with temperature, the minimum concentration being required at about 26° C. (82). Rates of block and of recovery also varied with temperature, in a way explicable by changes in the diffusion coefficient in the aqueous phase. It was concluded that the reaction between curare and its receptors is a thermodynamically reversible process and is so fast that it is obscured by the much slower diffusion process.

In a study of various agents which inhibit the contraction caused by acetylcholine in the rectus abdominis muscle of the frog, Kirschner & Stone (96) used methods of kinetic analysis previously applied by others to enzyme systems. They assumed that the speed of contraction was directly proportional to the concentration of a complex formed by combination of acetylcholine and a receptor substance. The analysis indicated that various curare-like agents combined with the receptor in competition with acetylcholine to a degree determined by the dissociation constants. Physostigmine also appeared to compete with acetylcholine for the receptor; this was in addition to its well-known antichlolinesterase action and was revealed only at high concentration after cholinesterase had first been inactivated by lower concentrations of physostigmine or by TEPP.[3] Atropine acted both competitively and noncompetitively.

[3] TEPP (tetraethylpyrophosphate).

A striking decurarizing effect of choline was investigated by Hutter (87). The decurarization was accompanied by an increase in amplitude of the end-plate potential without change in its time course and was possibly due to an increase in output of acetylcholine from the motor nerve endings. The normal concentration of choline in blood may be high enough to have a similar decurarizing effect (10). Decurarization can also be achieved by stretching a muscle. This is associated with an increase in the end-plate potential (101, 110). Much additional information on synthetic curarizing and anticurarizing agents appeared in a symposium (1) and in a paper by Pelikan & Unna (140). The biological role of quaternary ammonium compounds was discussed by Lilienthal (111). A review by Taylor (168) and investigations by Randall (142, 143) were particularly concerned with relationships between molecular structure and blocking action of various compounds.

Additional substances related to acetylcholine.—Many chemical analogs of the supposed junctional transmitter agent, acetylcholine, have recently been synthesized. These have been tested, for example, on heart muscle of *Venus* (177), on the arterial pressure of the dog, and on various mammalian tissues (156).

Koelle (99) has improved his methods for histochemical localization of cholinesterases and has been forced to revise some of his previous statements (98). He now reports that specific cholinesterase was found principally in the dendrites, cell bodies, axons, and terminations of cholinergic neurons, at the motor end-plates of striated muscle, and in low concentrations in sensory neurons. In general the specific and nonspecific enzymes were found to overlap less in their distributions than previously reported. For example, nonspecific cholinesterase was found in glial cells of sympathetic ganglia, but not in ganglionic neurons. This only serves to emphasize the special relationships of specific cholinesterase with neurons, although the enzyme also occurs in several nonneuronal locations. The distribution of cholinesterases in the nervous system was further considered by Burgen & Chipman (26) and by Feldberg (55).

Cholinesterases were reviewed by Whittaker (178) and by Holmstedt (83). The latter gives an extensive table of compounds with formulae and bibliographical references. "Tabun" is reported (83) to be a more potent anticholinesterase than even TEPP.[3] Poisoning caused by systemic administration of TEPP[3] was studied (39) and its mode of action at the end-plate was analyzed (40).

Effects of certain hormones on excised nerve-muscle preparations of the rat (170) have been ascribed to changes in acetylcholine metabolism (171).

Fibrillation.—Fibrillation in denervated muscle was found to originate in the end-plate region [Jarcho *et al.* (89)]. The frequency of fibrillary potentials was first increased and then decreased by both decamethonium and by *d*-tubocurarine, thus showing that both substances have excitatory as well as depressant effects (89). Fibrillation was also studied by Landau (104, 105) who showed that the frequency of discharge could be altered by applying steady currents. Brooks & Myers (20) reported that cholinesterase

concentration of muscles did not decline following denervation, so that fibrillation and sensitization to acetylcholine could not be explained by a loss of this enzyme as suggested by other authors [see (20) for references to conflicting evidence].

Transynaptic Excitation

Reviews on this subject which appeared during the year include a symposium led by de Castro, Feldberg, Heymans, & Bremer (5) and a summary by Lloyd of much of his recent work (116).

Presynaptic endings.—It has become increasingly apparent that a presynaptic ending, like other nervous tissue, is characterized by a lability in its properties, and that therefore the arrival of a presynaptic impulse does not always produce the same degree of change in the cellular environment. Eccles & Rall (46) have recently speculated that some of this lability might be associated with changes in volume of the presynaptic endings, similar to the volume changes which have been observed in giant axons of invertebrates following activity (74). Previous experiments on sympathetic ganglia suggest (*a*) that action in presynaptic endings becomes fatigued during prolonged repetitive activity, since failure of transmission is accompanied by a decline in acetylcholine production (21, 91), and (*b*) that presynaptic action becomes potentiated during certain phases of recovery from activity, since observations on prolonged facilitation cannot be otherwise explained (108). Lloyd (113) concluded that a similar phase of prolonged facilitation, which he observed in the spinal cord and called "post-tetanic potentiation," could also be explained by a change in the presynaptic fibers, specifically by an increase in their action potentials.[4] The postulate of an increased presynaptic action potential has now been challenged by Eccles & Rall (46). They found that changes in amplitude of the presynaptic spike potential, recorded with electrodes inserted into the spinal cord, did not correlate perfectly with prolonged facilitation, and did not correlate at all with an earlier facilitation which they discovered. These objections to Lloyd's suggestion seem at least partly irrelevant, since the newly described facilitation could well be due to mechanisms totally different from those underlying the later phases of prolonged facilitation.

New aspects of the phenomenon of prolonged facilitation have been added to those originally described, which included an increased effectiveness of impulses arriving at inhibitory as well as excitatory endings. Eccles & Rall (46) have recently reported that the negative synaptic potential evoked by a test volley entering the spinal cord is also increased in size during the period of facilitation, and Rosamond Eccles (48) has observed an increase in size of a positive wave which is evoked under certain conditions in sympathetic

[4] It is perhaps unfortunate that the adjective "post-tetanic" has become attached to this prolonged phase of facilitation. As originally observed in sympathetic ganglia, the phenomenon was readily detectable after a single conditioning volley (108); it seems likely that the underlying changes are also developed in the spinal cord by small numbers of impulses, although apparently masked by other factors.

ganglia by preganglionic impulses. Ström (166) was unable to demonstrate prolonged facilitation in spinal reflexes of cats when the conditioning or testing impulses were initiated by stretching a muscle instead of by electric stimuli as in previous investigations. Several possible technical reasons for this failure were suggested by the author. The powerfulness of prolonged facilitation was emphasized by Benson & Jefferson (9), who found that stimulation of afferent fibers from a muscle could activate nearly an entire motoneuron pool during the period of facilitation.

A possible role of prolonged facilitation in memory or in conditioned reflexes has been discussed by Eccles & McIntyre (45). Dorsal roots of cats were severed distal to the sensory ganglia. A month or more later the reflex responses to stimulation of dorsal roots were recorded electrically from ventral roots or from nerves to muscles. The number of motoneurons discharging impulses was thus found to be much less in reflexes on the operated than on the normal side, especially in monosynaptic reflexes. This suggested that the effectiveness of transynaptic excitation declined during "disuse." The effectiveness could, however, be at least partly restored by activity, for prolonged facilitation following repetitive stimulation was much greater on the operated than on the normal side. Of possible significance in problems relating to memory was the finding that facilitation declined much more slowly at the disused synapses than normally, lasting sometimes "for many hours." Quite different speculations by Young (183) concerning the basic mechanisms of learning were prompted by anatomical and behavioral studies in *Octopus*.

Environmental changes.—Changes produced in the environment by action in presynaptic endings are commonly referred to as the synaptic transmitter. This is the stimulus which evokes important changes in the postsynaptic neuron. In order to emphasize the possibly complex nature of the transmitter we quote, from the first volume of *Annual Review of Physiology* [Bronk & Brink (17)],

> Any change in the environment of a nerve cell will necessarily alter the basic structure of the cell and will, accordingly, tend either to excite or depress its activity. Transmission across a synapse would consequently be accomplished by the net effect of all the chemical, electrical, and resulting ionic changes which are produced by the presynaptic impulse.

The tasks implied in this statement still remain before us today, first to identify all the environmental changes occurring at a synapse, and second to determine the relative importance of each constituent change. The relative importance of each may not be the same at all synapses and under all conditions of acitivity. It is worth recognizing, for example, that when neurons are excited by synchronized volleys of impulses, as in much of modern neurophysiological research, there is a tendency to exaggerate the relative importance of brief components of transmitter action at the expense of more enduring environmental changes. The latter may accumulate in significant amounts only when impulses arrive over the various presynaptic fibers for relatively long periods in naturally random time relations; under these

natural conditions brief excitatory effects would summate less effectively than more persistent changes.

Since publication of the statement quoted above, evidence has accumulated which points strongly to acetylcholine as the predominant transmitter at the skeletal myoneural junction [e.g. Lilienthal (111), Fatt & Katz (51, 53)]. Even more important perhaps, has been the recognition that within the nervous system the transmitter may not be the same at all synapses, not even within a restricted region such as the spinal cord. This possible multiplicity of mechanisms has been emphasized recently by Feldberg (55), although he concludes that, if transmission is shown to be by chemical mediation at one location, it probably is chemical at other synapses also. We would not agree with even this restriction: all sorts of modifications seem possible, causing functional predominance here of one aspect of the environmental change, there of another, especially in view of the wide variety of morphologies found at different synapses [Bodian (4)]. Differences between transmitter substances at different synapses have been suggested by those who propose that acetylcholine is one of the transmitter agents in the central nervous system, in order to explain the uneven distribution of acetylcholine, cholinesterase, and choline acetylase [Feldberg (55); also (26, 99)]. Dissimilarity between synapses may also account for some of the differences in effects on various synapses and reflexes exerted by a given chemical agent, such as an anticholinesterase [(12, 29, 73) and Skoglund in (4)], an anesthetic (84, 141) or other pharmacological agent [e.g. strychnine (154), analgesics (84)], or lack of oxygen (97). It should be noted that several authors have questioned the assumption that all effects of anticholinesterases are due to their action on cholinesterase, thus casting doubt on these substances as tools for demonstrating a physiological role of acetylcholine (12, 73, 96).

The past year has witnessed a reversal of hypothesis by J. C. Eccles, a prolific and stimulating theorist of the synapse. Previously a proponent of the action current of presynaptic fibers as the sole transmitter agent, he now suggests that all transynaptic effects, excitatory as well as inhibitory, are chemically mediated. This change of view resulted from the observation, made in motoneurons with an intracellular microelectrode, that inhibitory impulses caused an increase in membrane polarization which was essentially the mirror image of the excitatory depolarization (15). Eccles found this difficult to reconcile with his previous electrical theories of inhibitory mechanisms.

The postsynaptic neuron.—Changes produced in the postsynaptic neuron by impinging impulses may be conveniently divided into (*a*) nonpropagated effects, (*b*) propagated impulses generated if local excitatory changes are great enough, and (*c*) recovery processes following the discharge of a propagated impulse.

(*a*) It has been known since 1946 [Lloyd (112)] that subthreshold excitatory effects on spinal motoneurons, produced by synchronized volleys of presynaptic impulses, subside exponentially with a time constant of about 4 msec. and are detectable, by tests employing monosynaptic reflexes, for

about 15 msec. This period of increased excitability is paralleled by, and presumably due to, a partial depolarization of the motoneurons (the synaptic potential), recorded indirectly by its electrotonic spread into ventral roots (44, 116) and directly by new techniques employing intracellular microelectrodes [Brock, Coombs & Eccles (14, 15); Woodbury & Patton (182)]. While it is thus clear that the excitatory effects caused by impulses reaching a synapse persist for many milliseconds, it is not yet agreed whether these enduring changes in the postsynaptic neuron result from continued action of the synaptic transmitter, such as a flow of current generated by prolonged polarization changes in the presynaptic endings [Lloyd (116)], or whether the depolarization of the postsynaptic neuron persists for a time after the end of the transmitter action [Eccles & Rall (46)]. It seems to us that recent observations with microelectrodes inserted into motoneurons, which show that the synaptic potential thus recorded is positive with respect to a remote indifferent electrode (14, 15, 182), cannot be explained by prolonged depolarization of the presynaptic endings, and that, therefore, the synaptic potential is probably generated, at least in part, in the membrane of the postsynaptic neuron.

Recent experiments suggest that the period of increased excitability and partial depolarization of motoneurons following subthreshold excitation, described above, may be followed by a period of subnormal excitability which has been named "subsynaptic depression" because it did not appear to spread away from the synaptic terminations under which it was generated [Brock, Eccles & Rall (16)]. The occurrence of another, more widely distributed subnormality was suggested by the observation of a slow positive potential which spread electrotonically into ventral roots following the negative synaptic potential evoked by subthreshold excitation. This positive potential was augmented by repetitive activity and showed two phases, like the positive after-potentials of peripheral nerve fibers [Eccles & Rall (47)].

(*b*) Lloyd (114) studied in considerable detail the spread of a propagated impulse over the surface of a motoneuron. This was done by recording the potentials generated on the surface and within the substance of the spinal cord by a volley of antidromic impulses. Lloyd concluded from these observations that conduction was slower along the dendrites than along the axon, in agreement with the earlier studies of Lorente de Nó (119) on the hypoglossal nucleus. He disagreed, however, with the conclusion of others that conduction is delayed at the axon-soma junction (7).

(*c*) Considerable information about the time course of recovery following the spread of a conducted impulse over a motoneuron was obtained in a careful study of the effects of impulses sent antidromically into the spinal cord over a motor root [Lloyd (114, 115)]. In the first paper components due to impulses passing over various portions of the motoneuron were identified in potentials recorded on the surface and in the substance of the spinal cord. By sending two successive antidromic volleys into the spinal cord, it was found that the intraspinal segments of the axons of motoneurons recovered their ability to conduct about as rapidly as do axons in peripheral

nerves, but that conduction of a second impulse across the cell body was blocked for a slightly longer time (about 1.7 msec.). A much greater lag in recovery was found in dendrites, which began to respond as early as did the cell body but could not give a fully normal spike potential for more than 120 msec. It is not yet known whether the block of conduction which was progressively dissipated during this long interval occurred at the junctions of the various dendrites with the cell body, or at various points along the course of the dendrites. In either case the impairment of dendritic conduction, lasting for times comparable with the subnormal period of peripheral axons and with the period of depression as tested reflexly, signifies that impulse conduction in dendrites normally operates with a very small factor of safety. Obviously this may have important integrative functions.

In his second paper Lloyd (115) was chiefly concerned with the recovery of the monosynaptic reflex response after a volley of antidromic impulses. Following activity the irritability of a motoneuron to transynaptic excitation was shown to be modified by two separable factors: (*a*) intrinsic polarization changes, analogous to the after-potentials and their associated recovery processes in peripheral axons, and (b) extrinsic changes due to the flow of after-currents. After-currents were defined as currents generated in a volume conductor, such as the spinal cord, as a result of differences between the after-potentials at different portions of a neuron. By means of such currents, events in one part of a neuron influence excitability in other parts. This recognition of an important factor in regulating recovery required reinterpretation of some earlier observations by other investigators. For example, it is now obvious that potentials recorded from volume conductors following the passage of impulses are related to after-currents and do not reveal the time course of the intrinsic after-potentials in particular parts of neurons as has sometimes been assumed. After-currents following antidromic impulses were not only recorded, but were also measured indirectly by their effects on reflex excitability of neighboring motoneurons. Following an antidromic volley, after-currents were found to flow from soma to axon for about 45 msec. and then in the reverse direction for about 75 msec.[5] These currents accounted for differences between the recovery cycles in intramedullary and extramedullary portions of the ventral root fibers.

After-currents were allowed for by Lloyd (115) in estimating the intrinsic recovery process in synaptic regions of the motoneurons. It was concluded that the intrinsic recovery process may consist simply of a single phase, passing smoothly from refractoriness immediately after an impulse into subnormality, which lasts about 60 msec. The analysis does not seem to exclude the possibility of still later phases of sub- or supernormality, but there is reasonably good evidence against an earlier phase of supernormality corre-

[5] In this discussion we have followed Lorente de Nó (119), Lloyd (114, 115) and others in what seems to be an illogical use of the word "soma," which literally means "body," to include the dendrites as well as the body of a neuron. "Soma" has thus been arbitrarily adopted, for apparent lack of a better alternative, to permit brief designation of all the synaptically excited regions of a neuron.

sponding to the first negative after-potential of peripheral nerve. This is in agreement with previous reports (66, 124).

Slow potentials.—Under this heading will be discussed certain action potentials, all slower than spike potentials, which have been mentioned above either inadequately or not at all.

Of fundamental importance to all studies in which slow potentials generated within the spinal cord are recorded by their electrotonic spread along spinal roots is the discussion by Lloyd (115) of the techniques for accurately measuring ventral root potentials. Required are roots of specified minimum length, remoteness of cut ends, and control of temperature and concentration of carbon dioxide around the root.

Electrotonic potentials evoked in ventral roots by stimulation of a cutaneous nerve were studied by Brooks & Fourtes (18). They observed not only the slow potential described by others (the synaptic potential, lasting 5 to 10 msec.) but also an additional later wave which lasted a considerable fraction of a second. In a second paper (19) the flexor withdrawal reflex was reported to correlate with the second rather than the first ventral root wave in time and in conditions for its elicitation (strong stimuli in unanesthetized preparations). The earlier wave (the conventional synaptic potential) was accompanied by a discharge sufficient to produce only an inconspicuous twitch in the leg muscles, not an effective withdrawal movement.

Bonnet & Bremer (12) have published an extensive investigation of slow potentials evoked by volleys of afferent impulses in the roots and on the dorsum of the spinal cord of frogs. The recorded potentials differed in important ways from those observed in mammals, presumably because of different anatomical arrangements: the frog, for example, appeared to have no monosynaptic reflexes. The investigations chiefly concerned slow negative root potentials, lasting 100 msec. or more. These resembled the fifth component of the dorsal root potential described by Lloyd & MacIntyre (117), but appeared in identical form on ventral as well as dorsal roots. On ventral roots, impulses were discharged when the slow potential elicited by dorsal root stimulation exceeded a critical level. The critical level for discharge remained constant as the height of the slow potential decreased with spontaneous deterioration of the preparation, with fatigue, or with application of ether, chloralose, or urethane. The critical level for discharge also remained constant as the slow potential increased after application of strychnine, curare, physostigmine or neostigmine, and during summation between two afferent volleys at short intervals. However, the critical level could be altered by other agents, such as barbiturates or atropine. Effects of physostigmine and neostigmine were thought not to be due to the anticholinesterase properties of these agents, because similar effects were produced by small doses of strychnine and curare and because the time courses of the slow root potentials were unaltered. The paper contains many other interesting observations, including a great prolongation of slow potentials by veratrine and rhythmic discharges and rhythmic slow potentials following strychnine. The

authors concluded that the slow potential observed on ventral roots represented a depolarization (synaptic potential) of the motoneurons by internuncial impulses and that impulses were discharged repetitively while this depolarization was above threshold. The slow dorsal root potential was interpreted as a retrograde transynaptic spread of a similar synaptic potential generated in internuncial neurons. Time relations and other features suggested that potentials recorded from the dorsum of the cord were also synaptic potentials generated in interneurons by afferent impulses, but that there was in addition another, faster mechanism by which afferent impulses excited interneurons to discharge before the start of the synaptic potentials. Thus afferent impulses were thought to have two parallel and independent effects.

Slow potentials in superior cervical ganglia excised from rabbits were studied by Rosamund Eccles. Records were taken with one electrode on the ganglion and the other on the postganglionic nerve (48, 49). Low concentrations of *d*-tubocurarine blocked conduction and revealed the familiar negative synaptic potential (duration, roughly 100 msec.) in response to a single volley of preganglionic impulses. The synaptic potential was followed immediately by a late negative wave, not previously described, which lasted about 3 sec. Increase in concentration of curarine depressed and finally almost completely abolished these potentials, revealing a slow positive wave (duration, about 1 sec.) similar to that previously found following curarization of ganglia excised from turtles (107). Effects of repetitive stimulation and of compounds related to curare were studied. Anticholinesterases prolonged and augmented the slow positive potential, suggesting a relationship to acetylcholine. This implies that, in the presence of high concentrations of *d*-tubocurarine, acetylcholine may increase rather than decrease the membrane potential.

Retrograde changes.—Changes in irritability of the cell body due to axonal transection were sought in tibial motoneurons of cats by Renshaw & Rosenbaum (145). Neither the two-neuron-arc reflex nor the action potentials evoked in the motor nuclei by antidromic impulses were altered during the first few minutes after cutting the tibial nerve at a considerable distance from the cord. Thus there was no evidence of retrograde changes of the sort sometimes assumed to explain the crossed-phrenic (Porter) phenomenon (cf. 147); explanations of this phenomenon in terms of blood gases and pulmonary reflexes have recently been offered (109, 146).

Despite the above failure to detect retrograde changes in motoneurons immediately after axonal transection, profound effects have been observed after longer times in sympathetic ganglia by Brown and his colleagues (22). Three weeks after a postganglionic nerve of the stellate ganglion was cut, no impulses were discharged over this nerve in response to preganglionic impulses; however, the nerve was still able to conduct when stimulated between the ganglion and the transection. Thus some change must have occurred in the synaptic regions, the nature of which is being further investigated (23).

Morphology of Nerve Cells

Nerve cells have been studied by a variety of histological and histochemical methods. Among studies employing the electron microscope (8, 139) are several which are particularly concerned with the laminated structure of the myelin sheath (58, 71, 139). Fernández-Morán's extensive electron microscopic survey suggested that all nerve fibers consist of one or more of each of two basic units: the neurofibril and a layer of membrane sheath (59). Gradients in the water content of nerve cells were observed by using x-rays and ultraviolet light (136), and in electron micrographs (139). Turgidity changes with activity were recorded in axons by Cragg (30) and changes in optical properties by Bryant & Tobias [(24), also Tobias in (4)]. Nucleic acid changes were followed during Wallerian degeneration (131, 132), after administration of vitamin B_{12} (6) and during hibernation (174). Maxfield fractionated nerve proteins (133). Inorganic ions were studied by Gillaspy (67) and by Hess & Chu (72). The enzymatic activities of degenerating and regenerating nerves have been compared (125).

Evans & Vizoso studied the growth of motor nerve fibers in rabbits during post-natal development; the nerve trunk must be connected to muscle for growth to proceed, but development is not blocked by excision of large amounts of muscle mass (50). Windle and co-workers reported that by inhibiting the formation of a glial barrier with Pyromen (a bacterial polysaccharide) a peripheral nerve can be made to grow into a cat brain (179, 180). Pyromen also promotes regeneration in the spinal cord (157).

The unimodal and bimodal fiber distributions noted in nerves to different muscles appear to relate to the presence or absence of spindles and their associated small nerve fibers (57, 102). The pattern of motor innervation in striated mammalian muscle has been studied histologically by Feindel, Hinshaw & Weddell (54) and both histologically and electrically by Jarcho *et al.* (90).

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SOMATIC FUNCTIONS OF THE CENTRAL NERVOUS SYSTEM[1]

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Introduction

With the gradual recognition of the existence of widespread autonomic representation at the cortical level both in man and animals, there have become crystallized, largely during the years 1951–1952, certain morphological correlates which serve to elucidate the functional interrelation between the two systems. Thanks to the work of Kaada of Oslo (1), Dell of Paris (2), and a group in this country led by MacLean, Delgado, Pribram, and Wall, it is possible to subdivide the cerebral cortex into two main regions (3 to 8): (*a*) the neocortex comprising centers on the lateral surface and contiguous gray matter within its sulci—centers which function through projections to and from the lateral nuclei of the thalamus and also through connections with other parts of the cerebral hemispheres; and (*b*) the older limbic system, which is made up of a series of medial and orbital structures.

MacLean points out that by Broca's definition (9) the limbic lobe lies within the boundaries of the limbic fissure.[3] If one used Papez's terminology (10), the cortical structures included in the limbic system are: (*a*) the pyriform area and cortex surrounding the olfactory striae; the posterior parts of the medial orbital and posterior orbital gyri would be included in the latter category; by definition the insula and the temporal pole are outside the limbic lobe, but their cortex lying contiguous to the rhinal part of the limbic fissure is cytoarchitecturally similar to the limbic cortex in this region and could justifiably on these grounds be included in the limbic system; (*b*) hippocampal gyrus; (*c*) hippocampus; (*d*) parasplenial gyrus; (*e*) cingulate gyrus; and (*f*) subcallosal gyrus. The subcortical nuclear structures known to be directly related to the limbic system include: (*a*) the amygdala, (*b*) anterior thalamic nuclei, (*c*) hypothalamus, (*d*) epithalamus, (*e*) parts of the

[1] The survey of the literature pertaining to this review was concluded in September, 1952.

[2] Dr. Fulton retired as Sterling Professor of Physiology at Yale in February 1951 to accept a newly designated Sterling Chair of the History of Medicine, also at Yale. Dr. C. N. H. Long succeeds him in the Chairmanship of Physiology.—Ed.

[3] "Le nom de *circonvolution limbique* que j'ai adopté indique les rapports constants de cette circonvolution avec le limbe de l'hemisphère; il n'implique aucune théorie; n'exprimant pas une forme determinée; il est applicable à tous les cerveaux des mammifères, à ceux qui ont un vrai corps calleux comme à ceux dont le corps calleux est nul ou rudimentaire (lyencéphales d'Owen), à ceux qui ont un vrai lobe olfactif, comme à ceux dont le lobe olfactif n'est qu'à l'état de vestige. Enfin, il a l'avantage de permettre de designer sans changement d'adjectif les parties qui se rattachent à la description de cette circonvolution: le grand *lobe limbique*, la *scissure limbique*, *l'arc limbique supérieur ou inférieur*, *etc.*" (9, p. 391).

basal ganglia, and (*f*) pontine structures; Wall & Davis (8) showed that projections from the temporal cortex pass caudally by way of a tract running toward the pons (see also 121).

The limbic system is thus made up of a group of functionally interrelated structures which send and receive projections to and from the medial nuclei of the thalamus and hypothalamus, a system which in early neural development is involved in affectively determined behavior. No region of the cerebral cortex, however, is exclusively concerned with any one function and, while the limbic system is predominantly autonomic in its affinities and the neocortex predominantly somatic, in each there is extensive overlapping since some autonomic responses are obtainable from the neocortex, and from the limbic system a limited number of reactions affecting somatic structures. The present review will concern itself chiefly with developments in the sphere of somatic motor function which have appeared since Hines' excellent summary in Volume 14 of the *Annual Review of Physiology* (11).

During 1951 and 1952 there have been a number of general publications bearing on somatic function. Most important is the volume issued in June, 1952 of *Research Proceedings of the Association for Research in Nervous and Mental Disease* covering the meeting on the structural organization of the nervous system held in December, 1950 under the chairmanship of Dr. Philip Bard (12). Attention is directed also to Denny-Brown's masterful disquisition on the frontal lobes (13). Another symposium most be mentioned, i.e., *The Biology of Mental Health and Disease*, just published by the Millbank Fund (14). More important for clinical neurology is the last volume of that invaluable Bailey-von Bonin trilogy, *The Isocortex of Man* (15); the first two dealt with monkey (16) and chimpanzee (17). For the experimentalist, the Olszewski atlas of the macaque thalamus (18) is already proving indispensable. The volume of Wayneflete Lectures of John C. Eccles on brain and mind (19) is about to appear at the Oxford Press (London), and I have myself published two general résumés on the subject, the Thomas W. Salmon Memorial Lectures (20) and the Francqui Lectures (21). Finally, attention must be directed toward another brilliant trilogy by Colle (22), Gastaut (23), and Dell (2), a monographic review which has just appeared under the significant title, "Corrélations entre le Système Nerveux Végétatif et le Système de la Vie de Relation."

Somatic Functions of the Limbic System and Related Subcortical Structures

The data which follow are drawn from the Kaada thesis (1), the Dell review (2) and also the recent reports of MacLean, Wall, Delgado, and their associates (3 to 8). Following localized chemical and electrical stimulation of the various elements in the limbic system, reactions occur in both the autonomic and somatic spheres—reactions relating to eating, situations of defense and attack, behavioral patterns associated with the animal's search for food or struggle for survival. The autonomic components of the reaction

included lacrimation, salivation, pupillary dilatation, piloerection, respiratory and cardiac changes, and, occasionally, urination and defecation. Thus MacLean *et al.* (5, 6) and Gastaut (23) have observed in some instances that stimulation involving the pyriform cortex, or the hippocampus and amygdala, resulted in the appearance of many of the more stereotyped responses. Comparison of these reactions with those resulting from local application of acetylcholine indicated that the electrical responses were not caused by stimulation of fibers of passage but were the direct result of stimulation of the centers themselves. In keeping with this, MacLean (24) now finds that stimulation of taste receptors of the tongue tends to cause localized electrical activation of the pyriform region of the cortex. Kaada, working independently, reports similar findings from stimulation of the amygdala and pyriform cortex (25). These reactions were demonstrated in detail through motion picture analysis presented at the Scandinavian Neurological Congress at Oslo in September, 1952.

For a detailed analysis of the effects of stimulation of individual elements of the limbic complex, i.e., the piriform cortex, the temporal tip, hippocampus, fornix, and aymgdala, the Kaada thesis (1) should be consulted, also the recent papers of Gastaut (23) and of MacLean, Delgado, and their colleagues (5, 6). Most of the reactions recorded are in the autonomic sphere and do not pertain to the subject matter of this review. A few words, however, must be added concerning the posterior orbital gyrus (area 13).

Orbitoinsular complex.—Recent interest in the limbic system and adjacent structures had its origin in observations of Bailey *et al.* (26, 27) that stimulation of the central end of the vagus nerve caused electrical activation of the posterior orbital gyrus, while stimulation of the gyrus is followed by respiratory effects, changes of arterial pressure, gastrointestinal activity, and other reactions in the autonomic sphere; attention was also directed to the region by the discovery that bilateral, isolated ablation of area 13 yields a conspicuous hypermotility in monkeys (28). These pioneering studies have been fully confirmed and much extended during the past few years (e.g., 29) Kaada (1, p. 60) has studied a 12-week-old chimpanzee, finding that respiratory effects are readily obtained from area 13 at a time when only the face area of the motor cortex responded, indicating that the older limbic system is excitable before neocortex. The human orbital cortex likewise has excitatory characteristics similar to those of the monkey and chimpanzee (30, 31, 32).

Davis has just published a detailed study on the effects of area 13 ablation (33) which confirms and considerably extends the earlier ablation studies (28), finding that the hyperactivity may be due to concurrent involvement of the tip of the caudate nucleus, but that the vasomotor changes are due to interruption of the direct unmyelinated orbitohypothalamic tract which Wall *et al.* (34) have demonstrated by the Glees method. Davis has also made the significant discovery that monkeys with area 13 ablated bilaterally readjust less well to high altitude exposure than do normal macaques, sug-

gesting that this region of the brain is concerned in adaptation of the body to low oxygen tension. Ablation of area 13 in human psychotics with subnormal psychomotor activity have, in many instances, restored the patient to a normal or nearly normal behavioral status (20, pp. 121–24; 35).

Afferents of limbic system.—Activation of the various centers in the limbic complex must depend in part on afferent influx from subcortical, and especially spinal, levels—this in addition to input from other cortical sources. Full discussion of the problem would take us beyond the limits of the review, but attention must be directed to the significant recent work of several investigators (37 to 46). Prior to their studies it had been known that the hypothalamus, especially the mammillary bodies, receives a large ascending projection from the ventral tegmental nucleus via the mammillary peduncle [for full discussion see (20, pp. 39 to 44)]; and Bronk *et al.* (37) had shown that stimulation of "medullary" nuclei activates various nuclei in the hypothalamic complex. In 1951–1952 it was shown by both Downman (38) and Amassian (43, 44, 45) that the large fiber elements in the splanchnic nerve project, via nucleus ventralis posterolateralis, to somatic areas I and II of the cortex at a focus corresponding with the trunk representation (at 22 to 36 m. per sec.); other slower fibers proceed to the thalamic and hypothalamic levels. According to Aidar *et al.* (46), this slower (6 to 10 m. per sec.) component of splanchnic impulses reaches the posterior hypothalamus and caudal portion of the thalamus on both sides. In a personal communication (11 July 1952), Downman writes that he has been mapping the splanchnic projection to the cerebellar "trunk" area, and he is satisfied that the activity recorded

> is not secondary to a reflex movement and, being recorded in decerebrate cats, can not be a volley reflected back from the cerebrum. The response has often been difficult to find and facilitation by a preceding volley may be needed to produce the big responses one associates with afferent volleys activating a lively cerebellum. . . . I must try to improve repeatability of the response and determine the types and paths of the responsible fibres. I find that at the cerebral level splanchnic-evoked responses interact with the responses due to stimulation of somatic nerves which activate the same cortical areas. By needling the internal capsule and also recording off the lemniscal paths in the brain stem one sees that interaction occurs at thalamic level also.

The ascending paths of the vagus have also been followed with notable success by Dell & Olson (40, 41, 42) who find both specific and nonspecific autonomic projections passing to the forebrain in the cat, the specific projections (homologue of the classical projections of the somatic system) passing to the posterior orbital gyrus (latency 8 to 10 msec.), thus confirming Bailey & Bremer (26), this after relay in the most medial part of the nucleus ventralis posteriolateralis (latency 5 to 6 msec.). The nonspecific autonomic projections, passing to regions which they have in common with the nonspecific somatic projections, have been traced to many parts of the brain stem, the thalamus and the basal ganglion. One group of projections (latency 8 to 10 msec.) passes to the lobulus simplex of the cerebellum (see 42, p. 479).

Since the hypothalamus, as well as the thalamus, project to various elements in the limbic complex, and since many of the projections are severed in the operation of frontal lobotomy, these afferent visceral projections assume increasing significance and they undoubtedly account for the fact that pain is relieved in man following such a surgical procedure (see 20, pp. 124–25). As Dell, Downman and also Bremer (47) have pointed out, these visceral afferents interact at various levels with somatic afferents; in commenting on the significance of this important disclosure, I can do no better than quote the colorful words of Dell (42, pp. 526–27):

> Toutes ces données, et plus particulièrement l'homologie de l'organisation des systèmes spécifiques afférents et efférents somatiques et végétatifs, et l'existence de régions communes, où des messages intéroceptifs et extéroceptifs peuvent se combiner, établissent l'unité fonctionnelle du système nerveux central. La carte detaillée de notre propre corps et du monde extérieur, que projettent sur le cortex tous les systèmes afférents spécifiques, n'acquiert un sens que par le jeu des interrelations au niveau de ces régions communes et par les controles qu'elles exercent: nous ne portons notre attention que sur ceux des messages qui ont quelque intéret pour l'organisme; cet intéret est guidé surtout par la nécessité impérieuse de maintenir l'homéostasie du milieu intérieur: c'est ainsi que les parties les plus evoluées de l'encéphale entrent au service des grandes régulations végétatives.

Somatic Functions of the Neocortex and Related Subcortical Structures

The limbic system is primarily concerned with the integration of activities, autonomic and otherwise, which have been evolved by the phylogenetically older parts of the forebrain. The neocortex, on the other hand, with its projection systems to thalamus, midbrain, and spinal cord, is chiefly responsible for integrations in the somatic sphere. Papez (10) and his followers, such as Yakovlev (36), MacLean (3), Colle (22), Dell (42), and Gastaut (23), are responsible for crystallizing this dual concept, and I intend to adopt it for purposes of exposition in this review.

Inhibition, suppression, extinction and spreading depression—The literature of neurophysiology has become confused in the last few years through the ill-advised introduction of new terms to describe phenomena of common origin and mechanism. "Inhibition" is the term which had been used universally to describe states of subnormal excitability both in the central and peripheral nervous system. States of reduced excitability follow activation in any nerve cell, and if one grants that activation can occur without a propagated disturbance having emerged from the cell itself (Lloyd, direct inhibition), then even the refractory period may be looked upon as synonymous with a state of inhibition. Excitability may be reduced by changing the milieu of the nerve cell. Thus the spreading depression of Leão (48, 49) may result from exposure of the cerebral cortex to the air, i.e., to cooling and dehydration, conditions encountered in any open stimulation experiments. As Marshall (50) has pointed out, such spreading depression does not occur when stimulation is brought about by the use of implanted

electrodes provided the animal is normally hydrated, is at normal body temperature, and without anesthesia (51). The late Professor Dusser de Barenne disclosed that when certain areas of the exposed cortex were stimulated the excitability of the motor cortex became markedly diminished and spontaneous electrical activity suppressed. The regions from which such suppression of activity was obtained were designated "suppressor bands." Recently it has been found impossible to demonstrate these inhibitory foci in the intact waking animal when the cortex is unexposed (51, 52, 53). The phenomenon, however, can readily be demonstrated on the exposed cortex; in these circumstances the bands in question are clearly ones of active inhibition and should be so described. Nevertheless, no one can deny that in the normal cortex one area when stimulated may inhibit another adjacent area; but the significance of the "bands" as such remains problematical.

The phenomenon of "extinction" (54) which follows stimulation of the exposed cerebral cortex is also seen in peripheral nerve although here in different temporal relation; but again there is no possible reason for attempting to distinguish "extinction" from inhibition. I believe, therefore, that it would serve the best interests of neurophysiology if the more recent terms were abandoned, and that all states of diminished excitability in the central nervous system should be regarded as synonymous with "inhibition." This point of view is implicit in Sherrington's writings even though he was in large measure familiar with the more recent disclosures just cited. A term such as "refractory period" should be retained for descriptive purposes, provided one recognizes that phenomena occurring in peripheral nerve are in no way different from those encountered in the central nervous system except in their time relationships.

Cybernetics.[4]—The same considerations apply equally to that jejune term "cybernetics" which explains nothing, offers nothing conceptually new, and has spread unhappy confusion among students, especially those of an engineering and mathematical bent. "Feed-back" thinking is of course the basis of Sherrington's proprioceptive system. Speaking as a medical historian, I should point out that Sherrington observed, described, and fully documented the phenomena which led him to formulate the proprioceptive concept, and he did not allow himself the specious comparison of the nervous system to a telephone exchange. Neurophysiology has been much handicapped by the introduction of this unfortunate term and there can be little question that progress will be fostered by its abandonment.

Spinal cord.—Since Hines based her discussion of the spinal cord in the last *Annual Review of Physiology* (11) largely upon recent morphological and clinical findings (especially Cohn's important papers, 55, 56), I propose

[4] After this manuscript had gone to press our attention was directed to an important paper by F. M. R. Walshe entitled "*The Hypothesis of Cybernetics*" (*Brit. Journal Philosophy of Science*, 161–163, 1951). In this instance I heartily agree with Dr. Walshe.

to limit this discussion to experimental work appearing within the last two years and more particularly the group of important papers which form a part of the recently published (June 1952) 1950 symposium of the Association for Research in Nervous and Mental Disease, and also to the valuable Hagbarth thesis (57) issued from Professor Granit's Institute at Stockholm.

Reflex reversals at the spinal level have long aroused the interest of neurophysiologists: thus, the same cutaneous nerve at one time may give rise to flexion of the hind limb, and by altering either the rate or the intensity of stimulation it may be caused to yield extension (58). This suggested that change of the parameters of the stimulus might result in predominant excitation of different fiber groups, i.e., in a given extremity large "touch" fibers might yield extension, and small "pain" fibers, flexion. The problem is by no means settled, but fresh light comes this year from Hagbarth who proves conclusively that another important factor must be taken into consideration, namely, the region of skin stimulated. He finds that (57, p. 53) "each of the extensor muscles studied [spinal cat] was excited from [skin areas on] most parts of the limb, but inhibited from a skin area over the muscle itself," while "each of the flexor muscles was excited from most parts of the limb but inhibited from a skin area mainly localized over the antagonistic extensor muscle. Thus it cannot be maintained that ipsilateral skin afferents evoke flexor excitation and extensor inhibition." The disclosure is an important one since it indicates that the geographical site of origin of the skin afferent determines the character of the response and that fiber size is probably less important in the case of cutaneous nerves than had been previously supposed.

It has long been recognized that a stretch reflex of an extensor (in either the spinal or decerebrate state) may be inhibited by contraction of the muscle itself (autogenous inhibition, 59, 60). Since the stretch reflex involves a monosynaptic spinal pathway it is significant that inhibition evoked from autogenous sources within the muscle may, within a few milliseconds, abolish discharge from the affected extensor motoneurons; it may similarly abolish monosynaptic reactions evoked electrically [Granit (61, 62)]. It is generally assumed that the autogenous inhibition thus evoked stems from the Golgi tendon organs, but precise identification of the autogenous receptors is yet to be determined with certainty. Lloyd (63), for example, feels that the autogenous inhibitors cannot yet be identified and reserves judgment.[5]

[5] After this manuscript went to press a series of additional papers by Granit and his collaborators are appearing. Granit & Job (63a), using monosynaptic testing, find when the gastrocnemius muscle is de-efferented that gamma fiber activity as recorded electrically may still respond to stretch, indicating that the motor innervation of the muscle spindles is subject to tonic reflex influence. This has been further confirmed by Granit & Kaada (63b) and by Granit, Job & Kaada (63c) who find that the muscle spindles are directly activated by the pinna reflex. Finally Granit & Ström (63d) show that with light initial tension stretch causes more initial facilitation before than after de-efferentation. Hence the spindles must have been co-innervated and

This raises the question of identification of the stretch receptor itself, and on this point fresh knowledge has just been presented by Kuffler (64). It had been suggested that, since the muscle spindle lay "in parallel" with the contracting units and would, therefore, be relieved of a stretch stimulus when the surrounding fibers contracted (59, 65), the spindle must be the stretch receptor. This had been fully vindicated experimentally by study of the frog's sternocutaneous muscle (which has only 15 to 25 fibers and one muscle spindle). Here, when the muscle was slightly stretched, the single afferent nerve fiber from the spindle discharged continuously, but when the adjacent muscle fibers contracted the spindle response ceased (65). Kuffler (64) finds the same to be true in a variety of situations involving the spindle, but he has also isolated the small motor fibers innervating the intrafusal fiber of the spindle, and he has disclosed that when they are stimulated the threshold of the spindle for stretch rises conspicuously, thus corroborating the view originally put forward by Leksell (66). Kuffler draws the conclusion that the responsiveness of any extensor to stretch is determined by the reflex activity of some, perhaps the majority, of the small-fibered system emerging from the ventral roots, and that only as such are they related to muscle "tonus." For neurophysiologists this is a most welcome reinterpretation of the data obtained by Kuffler's skillful recording methods (67; see also 68, pp. 49–50).

Insight into the workings of the spinal ventral horn cell (in cats) comes from Eccles (69) who has succeeded in directing a microelectrode with tip diameter of less than 1 μ directly into a spinal motoneuron. He finds that the potential difference between active and indifferent electrodes ranges at first between 50 and 60 mv.; then it falls and becomes sustained for many hours at *ca.* 30 mv. The spike potentials are identical in magnitude and time relations whether evoked antidromically or by monosynaptic excitation; with the latter, there is a brief small rise in the nerve attributable to impulses in adjacent axons. Eccles points out that the identity of the time course in spike potentials, both for antidromic and monosynaptic excitation, shows virtual identity of after-potentials which "indicates that the synaptic potential and after-potential does not survive an impulse, and hence is a catelectrotonus of the motoneurone." Much more can be expected from this important advance in electrical analysis of the spinal motoneuron and it also bids fair to elucidate the nature of the central inhibitory process.

There have been many other studies of spinal cord potentials during the period under review: Brooks & Fuortes (70) adduce evidence in support of Barron & Matthews' much quoted paper (71), reporting that prolonged afferent excitation causes steady depolarization of the motoneurons of the spinal cord, and that artificial depolarization of these cells by constant

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from this evidence it is now clear that the muscle spindles are, in fact, the stretch receptors of skeletal muscle. This conclusion is supported by evidence presented in another recent paper on stretch receptors by Hunt (63e).

currents results in augmented excitability and eventual discharge of the motoneurons in question. In a more recent paper it has been shown that strychnine activates spinal motoneurons by reducing resting polarization (72), this having been observed in the peripheral cut ventral roots of frogs. The cervical cord of cats has also been explored, and single unit recordings indicate that phrenic motoneurons fire continuously throughout the respiratory cycle, but the frequency of their discharge increases toward the end of inspiration (73).

In other spheres there has been a series of notable papers by Magladery *et al.* (74) on spinal reflex patterns in man in which it has been clearly established by electrical methods that knee jerk and stretch reflex involve, as in animals, a monosynaptic reflex arc. Denny-Brown's thoughtful comment (75, p. 154) about Magladery's disclosures may be quoted:

> Dr. Magladery has shown us something of the spread of the monosynaptic reflex in man—indeed a considerable achievement. In its interpretation some difficulties are bound to arise. In such mass effects it is doubtful, for example, if increase in latency need mean a change to another pathway with more synapses.[6]

There have also been studies of the mode of activation of spinal motoneurons by the suprasegmental levels. Brookhart (77) reports upon direct stimulation of the bulbar pyramid in cat and monkey, using a stimulator in which all parameters including form of pulse, rate, and train duration could be independently controlled, the responses being recorded electromyographically. His observations may be given in his own words (77, p. 172):

> Excitation of motor neurons by evoked pyramidal volleys requires repetitive bombardment of the internuncial pool. The duration of pyramidal stimulation which produces threshold muscle responses is characteristic of an entire muscle and varies for different muscles. This threshold duration is altered in a regular and significant fashion by changes in stimulus frequency and pulse form. Large, rapidly conducting pyramidal fibers have a high stimulating potency as indicated by the constancy of the latent period measured from the final pulse of a series; they terminate principally in relation to motor neurons controlling facial and digital muscles, and probably are responsible for the phasic element of pyramidal control. Small, slowly conducting pyramidal fibers have a low stimulating potency as indicated by the long duration thresholds of muscles activated by such fibers alone; they form the principal source of control over proximal limb muscles, and probably are responsible for the tonic element of pyramidal function.

Lindsley (78) discusses the influence of the brain stem on spinal motor activity and Austin (79) records his experience in studying the action of the reticular formation on spinal monosynaptic reflexes, finding that (p. 220)

[6] L. W. Freeman writes that his long-awaited monograph on spinal man will perhaps appear in the foreseeable future. Dr. Freeman can be reached at 1040–1232 West Michigan Street, Indianapolis 7, Indiana, and anyone interested in the reactions of spinal man should not omit to consult Dr. Freeman and to urge him on with his monograph (76).

facilitation of monosynaptic reflexes was seen to occur frequently with, and occasionally without, inhibition of the polysynaptic reflex. . . . When motoneuron discharge became pronounced, there was usually maximal facilitation of a liminal or supraliminal two-neuron reflex and inhibition of the multineuron reflex.

Postural reflexes.—Perhaps the most significant single disclosure concerning the postural reflexes is that the tonic neck reflexes are mediated, not from the neck muscles as such, but from the ligaments of the upper joints of the neck, especially the atlanto-axial and the atlanto-occipital joints (80). In labyrinthectomized, decerebrate cats the tonic neck reflexes can still be evoked after section of all muscles connecting neck or trunk with the head —this after bilateral section of muscular and cutaneous branches of the first three cervical nerves and after resection and complete denervation of the muscles in question. The response, however, is abolished ipsilaterally by unilateral circumcision of the first three cervical roots at their exit from the ligaments; and the reflexes are abolished in all four extremities by bilateral circumcision, even though the muscle and cutaneous nerves remain intact (80).

The tonic neck and labyrinthine reflexes have been studied by Tokizane and his associates (81) who have shown that these postural reflexes can readily be demonstrated in adult healthy human beings through an analysis of the rate of discharge of a single neuromuscular unit, a technique similar to that used by H. E. Hoff (see 81) some years ago for demonstrating the effects of tonic neck reflex on single unit discharge in the cat's soleus. Tokizane *et al.* also demonstrated neck and labyrinthine reflexes in human infants.

Hypothalamus.—In considering the somatic functions of the limbic system, some attention must be directed to the hypothalamus, even though it is an area primarily concerned with autonomic integration. Its importance is twofold: (*a*) its anatomical connections with the cerebral cortex (neocortex as well as the limbic system) are rich and varied, and (*b*) it is a region of the forebrain in which autonomic and somatic functions overlap, thus to establish (to quote Dell, 2, p. 525) "l'unité fonctionelle du système nerveux central." The hypothalamus, as Le Gros Clark originally pointed out (82), acts in relation to the limbic system in much the same way as the thalamus itself does to the neocortex, for the hypothalamus has its own afferent system ascending from spinal (83) and medullary (20, pp. 40–41) levels, and in turn it projects to the cortex. Within the year it has been established that a large, direct, unmyelinated motor projection passes from the orbital gyri to the ventromedial and lateral hypothalamic nuclei both in monkeys (34) and man (84). Direct projections, also unmyelinated, pass to the hypothalamus from the precentral neocortex (see 20, p. 62). Other parts of the limbic cortex are served by the well-known tract of Vicq d'Azyr which arises in the mammillary bodies and passes to (and from) the anterior nuclei of the thalamus, all hypothalamic projections appearing to be two-way systems.

Recent studies of the hypothalamus have been somewhat more fruitful

in the morphological sphere than in the functional, but it has been shown that vasomotor reactions from stimulation of area 13 are abolished when the hypothalamus is destroyed, while the respiratory reactions to such stimulation remain unimpaired (85; see also 20, p. 56). Stevenson *et al.* (86) have confirmed earlier findings with regard to obesity and increased food intake following hypothalamic lesions. They also report profound alteration of electrolytic and water metabolism; indeed, with posterior lesions (rats) a state supervenes that appears to be the opposite to that of diabetes insipidus (anterior lesions).

Evidence of the welcome resurgence of neurophysiology in Japan is to be found in the papers of Ban and his associates (87, 88) on hypothalamic stimulation (rabbit) in which they produce conspicuous sleep reactions from Kurotsu's "C-parasympathetic zone," finding that it is correlated with electrolytic changes, blood potassium decreasing and calcium increasing during sleep reaction, the reverse being the case in sham rage (Kurotsu's "B-sympathetic zone"). They conclude (87, p. 159): "The fact that sleep is controlled by physical conditions . . . rests in the balance between sympathetic and parasympathetic potential, and that balance is closely influenced by metabolism."

Reticular formation.—One of the most significant disclosures in the recent history of neurophysiology has been that of the governing role of the reticular formation in the coordination of posture and locomotion—this through the interplays of its vast facilitatory and inhibitory areas on both spinal neurons and on those of the cerebral cortex. Magoun and his associates (89 to 92) have been largely responsible for elucidating these important midbrain functions, but the clinical implication of their work has not yet been fully appreciated. It is now clear, however, that the poliomyelitis virus (93), as well as that of encephalitis, has a remarkable affinity for these nuclear masses and that this accounts for some of the bizarre symptoms encountered, especially in the early stages of these diseases. More recently the reticular formation has come to be recognized as the primary region concerned in the regulation of the rhythm of sleeping and waking.

Bremer (94) had originally put forward the challenging suggestion that the loss of consciousness of normal physiological sleep resulted from physiological or anatomical interruption of the great ascending pathways, for cats, as judged by electroencephalographic rhythms, seemed to slumber perpetually after the forebrain had been isolated by pontomesencephalic section—hence sleep must be the result of "functional deafferentation." This remained the orthodox interpretation until 1950 when Lindsley *et al.* (95) found after isolated lesions of the reticular formation that animals exhibited a marked degree of hypersomnia with diminished spontaneous activity during waking hours—a reaction which failed to occur when this area was spared. A similar conclusion is reached in a recent clinical study by Michael Jefferson who writes (96, p. 66):

Magoun and his school argue from these results that Bremer's conception is no longer tenable unless the concept of deafferentation be enlarged to include the reticular substance within its scope. They believe the latter plays the cardinal role in the preservation of wakefulness, by offering a constant background excitation directed toward the hemispheres, and in roundabout fashion by virtue of its facilitating effect upon lower motor levels. The great sensory tracts of the brain-stem are, they infer, only important in so far as they provide collateral channels, by means of which the spontaneous activity of the reticular formation may be enhanced. In the light of this new knowledge from the physiological laboratory, it seems not overbold to suggest that when parasomnic symptoms occur clinically with stem disorders, they indicate encroachment of disease upon the reticular substance.

The late Hugh Cairns in his posthumously published Horsley Lecture (97) offers a wealth of clinical data bearing out Jefferson's conclusions. Sir Hugh was somewhat less committal about the precise localization of the area concerned in the maintenance of consciousness, although he was prepared to place the vital center at the level of the midbrain. Reports of more recent experimental studies in animals will be found in the summaries of Lindsley (91) and Austin (92), but their findings alter in no way the conclusions originally reached by Magoun & Rhines (89).

The cerebellum.—Our concepts of cerebellar functions have been radically altered within the past few years. It now turns out that this perplexing region of the central nervous system has a high degree of functional localization which has been simultaneously demonstrated—and for the most part independently—by investigators in different laboratories (98 to 104). It has been pointed out that the regions in the cerebellum which receive connections from end-organs serving tactile, auditory, and visual impulses are those which receive projections from corresponding areas of the cerebral cortex and in turn project to them; thus every focus of the motor cortex which receives projections from specific regions of the cerebellum projects back to that part of the cerebellum. From the anterior lobe of the cerebellum one may elicit well-localized muscular reactions and from the same foci, either inhibition or excitation of the muscle in question, depending upon the rate of stimulation of the particular focus (98, 100, 102). Sharply localized inhibition of cortically induced movements can be evoked from the anterior cerebellum, and the mosaic of foci yielding these specific inhibitory reactions follows a definite pattern with the caudal segments being represented in the most rostral portion of the cerebellar anterior lobe (the lingula), the hind extremities in the lobus centralis, the upper extremities in the culmen, and the head and neck muscles in the simplex (somatic area I). This corresponds closely to the site of termination of the ascending spinocerebellar fibers from the parts in question; overlapping secondary motor representation has been demonstrated by Hampson (103) in the posterior lobe (somatic area II). The recently published maps of Hampson and his collaborators (104) should be consulted for details concerning the secondary motor fields.

Frequency.—One of the riddles of the cerebellum as yet unsolved is the

conflicting results concerning the influence of the rate of stimulation on the reactions of the anterior lobe. All are agreed upon the topographical arrangement of specific foci, but Nulsen *et al.* (98) found cortically induced movements and knee jerks in lightly anesthetized monkeys were facilitated by high frequency stimulation (80 to 100 per sec.), while low rates of stimulation (10 to 40 per sec.) of exactly the same focus yielded inhibition. They observed, furthermore, that when the dentate nucleus was destroyed only facilitation could be obtained at all rates of stimulation, and that when the fastigial nuclei were destroyed only inhibition could be evoked, again at all rates. They concluded that there must be two independent motor systems emerging from the cerebellum, one presiding over inhibition associated with the dentate outflow and another concerned with facilitation and associated with fastigial nuclei. Moruzzi, on the other hand, working quite independently of the Yale group, reached precisely opposite conclusions, i.e., high frequencies inhibited and low frequencies facilitated (99, 100). This discrepancy is perhaps to be explained by the fact that Moruzzi was using decerebrate cats and studying localized inhibition or facilitation of either the decerebrate rigidity or the myotatic reflex, while Nulsen was studying cortically induced movements in cats, monkeys, and chimpanzees with intact nervous systems. The conditions of experimentation being so radically different, there would seem no basis for viewing with skepticism the results or conclusions of either group of investigators. Snider has also studied the problem of frequency of stimulation (102, p. 274) but has not yet published his results in detail.

Livingston (104a) has likewise observed striking effects of changing frequency of stimulation of the cortical eye fields (area 8). Thus on stimulating at 60 per sec. he noted conjugate deviation of the eyes to the opposite side, whereas when precisely the same focus was activated at 10 per sec. there was conjugate deviation of the eyes to the same side. Various autonomic effects were also responsive at different rates of stimulation.

Spontaneous discharges from the surface of the cerebellum are selectively susceptible to ischemia, and it has been inferred from this that the waves in question must arise from functionally different motor systems (105). This is in keeping with the fact that both excitation and facilitation can be obtained from identical foci, depending upon stimulation frequency. It is interesting that some of the ascending fibers in the pyramidal system apparently terminate in discrete fashion in the cerebellum (106, 107).

The part played by the cerebellum in the integration of visual reactions has again come up for discussion (108). It has been found that the tuber vermis, a midline structure lying just rostral to the pyramis, responds, electrically to stimulation of both the visual area 17 (occipital cortex) and the frontal eye fields (area 8). This is in keeping with the fact, disclosed some years ago (but since then not referred to in the cerebellar literature), that isolated ablation of the pyramis (which would involve the projections

from the tuber) caused monkeys to misgauge distances (109, p. 518).[7] Thus:

> The only symptom detected in three monkeys from which the pyramis was ablated was a rather surprising inability to arrest forward locomotion in time to prevent crashing headlong into a clearly visible obstruction. When set loose in a corridor, a monkey three or four days after the pyramis has been removed would run full force into a door at the end. The significance of this has not yet been established, although it is possibly to be correlated with the fact that the pyramis is the most responsive part of the cerebellum for eye movements. Faradic stimulation of the pyramis gives rise to upward movement of the eyes; and it is possible the pyramis may be concerned in some way with the integration of proprioceptive data essential for gauging distance.

The mechanism underlying cerebellar seizures has also been made the subject of renewed study (110). Such seizures may occur in cats after complete removal of the motor area, and after destruction of most of the remaining cerebral cortex; such seizures may occur likewise, and in complete form, after section of one basis pedunculi, one pyramid, dorsal nerve roots to an extremity, the vestibular apparatus, both eighth nerves, and the upper three cervical nerves of both sides. After complete splitting and removal of the cerebellum from one side, the seizures are confined to the undamaged side. Clark & Ward conclude that the seizures are not dependent upon incoming afferent impulses, but they were not able to discover from what elements in the cerebellum they arise, or what efferent channels are responsible for conveying the abnormal excitation.

Cerebral cortex.—Studies of the somatic function of the cerebral cortex have been advanced notably during the past year through two general approaches: (*a*) study of parameters of electrical excitability supplemented by chemical stimulation of foci in different regions of the cerebral cortex and related subcortical structures (8); and (*b*) training studies in the higher primates before and after regional ablation of circumscribed cortical areas. The latter investigations are described in some detail by Dr. Harlow in the present volume of the *Annual Review of Physiology* so that they will be only briefly touched upon here.

Although many workers in the field have come to appreciate the great importance of controlling the parameters of stimulation in any study directed toward the nervous system, central or peripheral, adequate stimulators in which the rate, shape, duration, and intensity of individual current pulses can be independently controlled have been of recent date. Lilly (111, 112), who has been engaged for nearly five years in a protracted study along these lines (in which, through an ingenious technique involving the use of a battery of closely arranged electrodes, the stimulation parameters of each are readily controlled) finds that (112, p. 320):

> the quantity of electricity in a stimulus train at threshold (coloumb threshold) is less (despite a larger current threshold) for shorter duration pulses than for longer duration pulses, in the range covered, at all repetition frequencies investigated. These

[7] The observations were made in 1936 with R. S. Dow but have remained unpublished save for this reference to them in my book.

observations suggest that long duration pulses may waste large quantities of electricity which transport ions not useful in the excitation process, and which may lead to cellular injury in the cortex.

The results suggest (*a*) that certain parametric regions, i.e., those ranging between an upper and lower limit of electrical wave form, are responsible for stimulating principally the efferent cells or fibers in the cortex; (*b*) that other regions in the parametric scale stimulate both cortical cell groups and efferent systems; and (*c*) that long periods of stimulation by unidirectional rectangular pulses injure first the cell groups in the immediate proximity of the stimulating electrode, and later such unidirectional currents destroy the efferent projection system itself. Lilly's reports well repay searching analysis.

Delgado (113) has likewise given attention to stimulation parameters both in relation to the motor cortex of the waking cat (stimulated through the use of implanted electrodes), and also to the so-called "hidden motor cortex" studied with implanted electrodes (114). Using a battery of 14 to 24 aseptically implanted electrodes, he finds—as had Lilly—that reaction threshold of the waking animal was profoundly influenced by different anesthetics but that the movements evoked were similar in character for reactions from both the lateral surface and the so-called hidden motor cortex. Spontaneous activity of the animal decreased or even completely blocked electrical responses. When purposeful reactions were elicited, and the animal prevented from attaining the seeming goal, they acted "in a logical and adequate manner for avoiding the obstacle in question." Drinking and ingestion of milk resulted from stimulation of the medial part of the presylvian sulcus; through such stimulation the animals could be induced to take larger amounts of food than they would consume spontaneously.

Delgado made two other incidental observations of great interest, namely, that on no occasion did stimulation of the motor area appear to cause pain or disagreeable sensations, and that evoked motor responses of the face did not alter the course of spontaneous walking movements—this being in striking contrast to reactions which are evoked from some parts of the temporal lobe. "Arrest" reactions also follow activation of certain points in the buried cortex. In a second paper on the subject Delgado (114) estimates that more than half of the excitable cortex is buried and that there exists precise motor representation in the hidden areas, the hind limbs being represented in the cruciate sulcus; forelimbs, neck, and face are in consecutive areas, extending from the superior to the inferior part of the presylvian sulcus. It was noted (7) that minute injections of acetylcholine disclosed similar specificity of localization. In this way the possibility of spread of current to adjacent cortical projections from the superficial cortex was ruled out.

Delgado also considered the problem of stability of cortical points, pointing out that his findings agreed with those of Clark & Ward (115; see also 11, pp. 400–1). Delgado states (114):

Stimulation of one point evoked the same response in all the studies performed over several months. But stimulation of this point produced different results on the same

day if some of the experimental conditions were changed. Parameters of stimulation, activity and posture of the animal were the most important factors.

The importance of initial posture is especially stressed, since the responses may change or even reverse according to the posture of the cat at the onset of stimulation.

In discussing the relation of the hidden cortex to the so-called secondary motor area of Garol (116), Delgado asks:

> What is the meaning of the hidden motor cortex? Could it be a third motor area? As we suggested in a previous publication, the cortex buried in the frontal lobe, rather than a new motor area, may be a bridge uniting the so-called primary area located around the gyri sigmoideus, anterior and posterior, with a nominal secondary area situated in the inferior portion of the anterior ectosylvian gyrus. The surprising fact is the multiplicity of representation: from three different regions, two superficial, one hidden, responses of the face, neck, etc., are evoked by electrical stimulation.

Some of the supplementary motor areas may be primarily sensory and discharge to the motor area, but the fact is that they exist, and they are still responsive after ablation of the primary and secondary motor areas (114)—hence they must have their own channel of discharge. This may account for the dramatic recovery which occurs after regional ablation of the primary areas. As Delgado remarks, "The existence of the hidden motor cortex may be one of the reasons why symptomatology is meager and functional recovery good after destruction of the superficial motor cortex in cats." These findings are in agreement with data presented by others, e.g., Magoun *et al.* (117), who reported that chewing is localized in the inferior part of the external bank of the presylvian sulcus and rhythmic stepping in the contralateral forelimbs in the base of the sulcus.

The pyramidal system.—The wide discrepancy between the number of Betz cells and the number of fibers in the pyramidal tract has proved highly perplexing to neurologists. To be sure, there are many fibers of small diameter in the pyramids, many of which must have their origin in smaller motor cells of the cerebral cortex; only the cells of Betz, however, degenerate when the pyramids are severed. Antidromic stimulation of the pyramids at the level of the olive evokes on the cortex potentials of wide distribution which include all of Dusser de Barenne's sensorimotor cortex (118). From this the conclusion was drawn that the pyramidal tracts took origin from the entire precentral and parietal cortex (119). This seemed to account for the discrepancy just mentioned, but something of a bombshell will no doubt be felt when the as yet unpublished studies of Brodal & Walberg appear on the ascending fibers in the pyramidal tract of the cat (107).

Their evidence, which some regard as convincing, is based on horizontal silver impregnation of the brain stem (method of Glees). Lesions of the lateral or ventral corticospinal tracts cause ascending degeneration in both pyramids and in the cerebral peduncles, and terminal degeneration was found in the pontine gray matter. Lesions restricted to other areas of the

spinal cord fail to show degeneration of this type. Such ascending fibers may take origin from levels of the cord as far caudal as L5, but the main contribution comes from the cervical cord. These ascending fibers, moreover, vary widely in size and Marchi sections indicate that many of them are myelinated. The authors estimate that the ascending component in the pyramids amounts to about 4 per cent of the total number of pyramidal fibers. Some of the degenerating fibers have been traced up to the cerebral cortex, being found in the sensory and motor areas, the largest proportion passing to the sensory cortex. The topographical organization of this direct spinocortical pathway is similar to that of the corticospinal tract. Brodal & Walberg believe that the fibers in question mediate cutaneous impulses principally, and that fibers originating in the nuclei of the dorsal funiculi are probably proprioceptive in nature. They suggest, further, that the new pathway may be concerned in the mediation of proprioceptive reflexes such as the placing and hopping reactions. Some experienced histologists—H.-T. Chang, for one—who have had experience with the Glees method, and Dr. Glees himself, are skeptical of the interpretation placed on these findings, but no one can pass final judgment until the full text of this challenging work by Brodal & Walberg becomes available for detailed scrutiny.[8]

In 1939, Dusser de Barenne & McCulloch (120) found that after complete destruction of the thalamus ascending impulses still reached the cortex and they concluded that they must pass by the internal capsule. Since there were no known ascending systems that did not pass through the thalamus and hypothalamus, they also concluded that the impulses which they were studying must somehow reach the cortex by the internal capsule without having synaptic connections in the better known thalamic centers. They did not, however, suggest that the impulses in question passed up via the pyramids. This is what they reported (120, p. 623):

> In two other similar experiments no such spikes appeared and the autopsies revealed that in these monkeys not only was the thalamus removed, but in one case the posterior limb of the internal capsule interrupted, and in the other the medial fillet just below the level of the thalamus. From this evidence it follows that in the nucleus cuneatus originate neurones, whose axons run through the internal capsule directly to the sensory (arm) cortex. In other words, there exists a direct cortical fillet.

[8] Since this was written Kaada sends word (as yet unpublished) that ascending impulses can be recorded (from microelectrodes in the isolated pyramid) on stimulating the skin of the extremities and that the majority of such impulses arises in the contralateral forelimb; the potentials do not descend from the higher levels "since they persist after section of the pyramids just above the recording electrodes and are abolished after section caudal to the same electrodes. The majority of cutaneous impulses in the pyramids ascend in the 'cortico-spinal' tract (or perhaps rather tr. spinocorticalis!)." It is interesting in this connection that Malis *et al.* (119a) find that action potentials from stimulation of proprioceptive nerves from muscle can be detected in area 4, and it is possible that some, at least, of these reach the cortex through the ascending fibers of the pyramids.

Extrapyramidal motor projections.—It has long been recognized that volitional movements can be executed after bilateral section of the pyramids, and experimentally one can evoke motor reaction by stimulating the precentral cortex of such a preparation (monkeys and chimpanzees). The origin and destination of the extrapyramidal motor projection responsible for mediating these responses is too little known, but a most notable monograph on the corticopontine projection of macaques has just appeared (121). The authors report that the frontal, parietal, occipital, and temporal lobes all contribute to the system, and they stress the fact that all three parts of the frontal lobes, i.e., motor, premotor, and prefrontal, participate. The fibers terminate in discrete parts of the pontine nuclear complex in precise topographical fashion and with little overlapping; the frontopontine in the penduncular, paramedian, and dorsal pontine nuclei; the parieto- and occipitopontine in the peduncular, the lateral, and dorsolateral nuclei; while the temporopontine fibers end apparently exclusively in the dorsolateral pontine nuclei. The cerebellar vermis appears dominated by the fronto- and temporopontine elements, while the neocerebellar structures (the cerebellar hemispheres) appear governed predominantly by the parietal and occipital components. It is pointed out further that these findings are in good accord with the most recent physiological disclosures concerning functional localization in the cerebellum, and special mention is made of the work of Adrian, Hampson & Snider (summarized above).

Further light on the site of termination of extrapyramidal motor projections has been obtained by strychnine neuronography (122); thus on activating under Dial anesthesia the macaque's premotor region, i.e., area 6 of Brodmann, electrical activity was recorded in the subthalamic nucleus, substantia nigra, tegmentum of midbrain and pons (ventral and dorsolateral portions), red nucleus, and the central grey. The authors conclude (122, p. 90) that "there exists an important pathway from area 6 to the spinal cord by way of the cortico-reticular and reticulo-spinal fibers," and that area 6 can thus "act independently of, as well as in association with, area 4 in the cortical control of posture and motion."

Ipsilateral representation.—The problem of ipsilateral representation in the cerebral cortex has again been studied in an attempt to elucidate the basis of the return of motor function following hemispherectomy in children (123). In chimpanzees it had been found some years ago (124) that ablation of the leg area caused contralateral motor paresis from which the animal gradually (but never completely) recovered; when the second leg area was removed a notable increase in deficit occurred in the ipsilateral extremity. The new studies were based on a quantitative method (125) for testing power and dexterity in the upper extremities of monkeys; following ablation of one hand area there was conspicuous impairment of the ipsilateral as well as the contralateral extremity, but the ipsilateral recovered more rapidly. Similar reactions have been observed in children after hemispherectomy (126, 127). The new experimental findings (123, p. 1191) "are conso-

nant with the statement that 'residual function must depend on residual cerebral tissue'" and they lend support to the suggestion that after hemispherectomy the ipsilateral fibers play an important role in the considerable power and use which patients—especially the younger patients—regain in the limb contralateral to the lesion. On the basis of Marchi studies in monkeys and in one human subject it was estimated that 15 per cent of the pyramidal projection is ipsilateral (123). These findings are also consonant with the fact that ipsilateral motor and inhibitory reactions can be evoked from certain foci on the precentral cortex (128).

In another recent study on ipsilateral representation (129) it is reported that ipsilateral movements of the upper and lower facial muscles can be obtained on the macaque under very light anesthesia, and that the area for ipsilateral movement is distinct from that for the contralateral. Lauer (129) also obtained ipsilateral responses from motor area II on the superior lip of the lateral fissure.

Frontal cortex.—Since Dr. Harlow is giving detailed attention to the frontal lobes in his chapter of this volume of the *Annual Review of Physiology*, I shall merely touch on several themes with which he does not deal. The regional reactions to stimulation have been dealt with earlier, but one must mention the recent paper of Hess *et al.* (130) in which it is shown that, by the use of implanted electrodes, various somatic and autonomic responses may be obtained from the orbital and cingulate gyri—responses similar in nearly all respects to those described earlier in this review (1, 2, 5, 6, etc). Thus they noted salivation, pupillary effects, twitching of face, lips and vibrissae from the orbital gyri, and inspiratory effects. These observers insist, however, that the cingulate and orbital gyri are not to be regarded as autonomic centers in the cerebral cortex, but rather as sensory areas, and that the reactions obtained "are responses to subjective sensations aroused by stimulation." This dogged refusal to admit the existence of autonomic integration centers at the cortical level is the more surprising since every argument used in discrediting autonomic cortical centers could be applied with equal relevance (or lack thereof) to the hypothalamus itself. The existence, moreover, of a direct orbitohypothalamic projection makes it quite clear that the posterior orbital gyri are, among other things, centers of autonomic integration.

The frontal cortex also assumes importance for quite another reason, namely, that lesions restricted to either the orbital gyrus or the anterior cingulate have proved highly effective in dealing with certain types of mental derangement. Our present state of knowledge can be summarized as follows (20, pp. 127–28):

> In conclusion it may be said that surgical intervention for the relief of otherwise hopeless psychoses has proved a most efficacious therapeutic tool. . . . Within the past three years there have been two notable developments: (i) the use of a more restricted operation, and (ii) adaptation of the operation to the nature of the mental illness. It seems clear that the depressed patient and the schizophrenic with subnormal

psychomotor activity should have a resection of the posterior orbital gyrus or an interruption of its projections, while the agitated, aggressive, and overactive psychotic should have either a cingulectomy or a topectomy involving areas 9 and 10. With the orbital surface lesion and the cingulectomy there is no intellectual impairment, while some degree of intellectual impairment inevitably follows upon a lesion of the lateral surface or section of its projections. . . .

The fibers which pass through the medial ventral quadrant appear to be those primarily concerned with the relief of intractable pain, and since their interruption can readily be achieved by electrocoagulation and since damage to tissues is minimal with this procedure and there is no trace of intellectual deficit following it, this would seem to be the operation of choice for dealing with pain.

There is much more to record than is possible in a summary such as this. Somatic sensory problems have been largely omitted and other contributors to this year's volume will make reference to the various important contributions to electrophysiology. I have in mind particularly those of Eccles (131), Chang (132) and Bremer (133), all of whom have devoted their attention in recent months to the source and mechanism of electrical potentials, both in the peripheral and in the central nervous system. They differ on certain points of interpretation. Thus, Chang favors the view that recorded potentials from the cerebral cortex involve circuits between the cortex and the thalamus—circuits of proved existence since the latent period of stimulation involves a delay of less than 6 msec. In view of this circumstance and the fact that anesthetics do not delay the response, he concludes that the responses in question stem from cortical neurons which impinge upon the thalamus. Bremer's studies coincide with those of Chang but he believes that there is a second system, slower to respond, which arises from the internuncial neurons of the cortex.

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VISCERAL FUNCTIONS OF THE NERVOUS SYSTEM[1,2]

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In spite of the general impression that visceral functions are more or less autonomous, stimulation or destruction of parts of the central nervous system has been known for more than a century to affect the activity of visceral organs. Only in recent years, however, have the central controls and conducting paths for visceral functions been extensively investigated. Difficulties lie in the fact that central visceral representation, particularly at the subcortical levels, are apparently diffuse and not ordinarily confined to a definite, known anatomical entity. The diffuseness is in part accounted for by the relatively crude methods of investigation, which necessarily involve massive extirpation or high current of stimulation, and is also in part related to the multiple collateral systems and the numerous relays usually concerned with integration of the intricate vegetative functions. The latter renders the classical degeneration method inapplicable in these studies.

It has been found difficult, at times, to interpret the visceral effects obtained by electrical stimulation of the central nervous tissue, since, on many occasions, two opposite types of response are elicited from the same region when the frequency or the intensity of the stimulus is altered. What, then, constitutes a "physiological" stimulus? It may be that many of the central visceral mechanisms have essentially regulatory functions, and are capable of initiating either type of response depending upon the nature of the afferent stimulus. Nevertheless, the accumulated knowledge on the central control of visceral nervous functions has already proven useful in the physiological, clinical, and psychosomatic fields.

Cerebral Cortex

Cortical stimulation.—Electrical stimulation of various cortical areas for visceral functions has continued to be a subject of interest to physiologists.

[1] The survey of the literature pertaining to this review was concluded in June, 1952.

[2] The following abbreviations are used in this review: TEPP (tetraethyl pyrophosphate); PPS (phosphopyristigmine); DFP (di-isopropylfluorophosphate); PAH (para-aminohippurate); Tm_{PAH} (transfer maximum of PAH); Tm_G (transfer maximum of glucose); TEAC (tetraethylammonium chloride); GFR (glomerular filtration rate: manitol clearance); RPF (renal plasma flow: PAH clearance).

[3] I am indebted to Mrs. E. Lopat and Mr. E. Meyerhoff of the Medical Library at Columbia University College of Physicians and Surgeons, New York City, for their assistance in this review.

Thus, Hess *et al.* (1) obtained autonomic effects from both the orbital and cingular areas of the feline cerebral cortex. Weak stimulation generally produces respiratory inhibition and a fall in blood pressure, while stronger stimulation yields the reverse. Still stronger stimulation results in marked excitement accompanied by hypertension, pupillary dilatation, and paroxysmal tachypnea. The effects are interpreted as the result of nonspecific irradiation to subcortical autonomic centers and are considered as incoordinate, rather than as part of a regulatory process. On the other hand, Hoff *et al.* (2) regarded the circulatory alterations which result from cortical stimulation as a significant mechanism whereby the cortex may participate in the autonomic regulation. These authors extended their observation to the ischemic effect on the kidney following electrical stimulation of foci on the anterior sigmoid gyri in the cat. The ischemic change is limited to the renal cortical tissue and abolished by interruption of its nerve supply. The actions of the most rostral part of the digestive tract during ingestion of food, which Babkin & Van Buren (3) called the "feeding pattern," are reproduced by electrical stimulation of the cerebral cortex. Mastication, respiratory inhibition, salivation, swallowing, esophageal contraction, and inhibition of antral motility are the typical responses following stimulation of the anterior composite gyrus. However, the important centers for the regulation of feeding habit appear to reside in the hypothalamus (36, 37). A review by Kaada (4) of the excitatory actions of the cortex on various autonomic effectors has appeared as a supplement of *Acta Physiologica Scandinavica* in which he also reported the representative cortical areas for pyloric antral activity, pupillary response, piloerection, salivation, micturition, and defecation. Wall & Davis (5) have analyzed the cortical autonomic effects in cats, and found that there are three distinct descending pathways: (*a*) the response elicited from the sensory-motor cortex is independent of motor activity or hypothalamic destruction, and disappears only after pyramidal section; (*b*) the vasomotor response from the posterior orbital surface and anterior insula is mediated through the hypothalamus, while the respiratory effects from the same area depend upon the integrity of the caudate nucleus; and (*c*) the response from the temporal lobe is unaffected following hypothalamic or pyramidal destruction. Using the electroencephalograph, Jasper *et al.* (6) have carefully mapped the corticofugal projections from the frontal, temporal, and occipital region to the diencephalon and brain stem in the monkey.

Cortical ablation.—Adey (7) has made degeneration studies in the hippocampal formation following lesions in the cingulate cortex of the rabbit. Chronic lesions in these cortical areas result in an increase in rate and depth of respiration which persist for 10 to 20 min. with an alteration in behavior in some animals. Adey & Meyer (8) have made similar studies on the monkey. In a review, Gastaut (9) stressed the importance of rhinencephalon for integrative expression of the visceral and somatic nervous functions, not only for the maintenance of constancy of the internal environ-

ment but also for survival in changing external events. Smell, according to Gastaut, plays a very important role in the total behavior of the animal.

Funkenstein *et al.* (10) reported that autonomic and psychologic changes occur *pari passu* in mentally ill patients under psychotherapy, electric shock, insulin shock, or other types of stress. Patients with chronic schizophrenia show slight, transient hyperreaction to epinephrine and Mecholyl (acetyl-β-methylcholine bromide) after superior and orbital topectomy, suggesting a release of cortical inhibition of autonomic functions [Glaser (11)]. Landis (12) claimed that patients, following psychosurgery, show less vigilance, zeal and anguish; but there is no demonstrable loss of intelligence, especially if surgery is confined to the more anterior portion of the frontal cortex.

Cortical representation of visceral afferents.—Amassian (13, 14) stimulated the splanchnic nerve in rabbit, cat, dog, and monkey, and found with the "evoked potential technic" that the visceral afferent projection does not differ in any important respect from the somatic projection other than in its peripheral origin. Similar findings have been previously reported by Downman (15). The numerous points of similarity between somatic projection and the fast component of the splanchnic afferent projection have been emphasized, such as the form and latency of the primary response, recovery of excitability, and periodicity of late waves, all of which suggest a similar type of synaptic organization. The primary cortical responses due to activation of Aβ splanchnic afferents, are localized largely in the trunk region of the contralateral sensory cortex (also of the homolateral cortex in the cat, but of a smaller amplitude), and are abolished following section of the posterior columns. However, the secondary, generalized responses mediated by the splanchnic Aγ-δ group are dependent upon both the anterolateral and the posterior columns. These findings have been essentially confirmed by Aidar *et al.* (16). They further observed that the faster impulses traverse the homolateral fasciculus and nucleus gracilis, the internal arcuate fibers, and the contralateral medial lemniscus to reach the contralateral nucleus ventralis posterolateralis of the thalamus. Much slower impulses ascend in the region of the lateral spinothalamic tract of the spinal cord bilaterally, and reach the posterior hypothalamus and the caudal portion of the thalamus. These authors inferred that these impulses are related to visceral pain, destined for reflex centers in the hypothalamus and also for conscious level through the thalamus.

Using the same "evoked potential technic," Patton & Amassian (17) localized the chorda tympani receptive zone to a 5 to 10 mm.^{2} cortical area on the orbital surface of the hemisphere, superior to the rhinal fissure and rostral to the anterior ectosylvian fissure. This projection zone is rostral and lateral to the tactile receptive zone for the face, but overlaps extensively the tactile representation of the tongue. These findings, according to these authors, are consistent with the hypothesis that taste pathways parallel and overlap the tactile pathways from tongue and face. Working on the "encéphale isolé" cat, Zanchetti *et al.* (18) demonstrated that spontaneous

cortical spindles and strychnine spikes are eliminated or reduced appreciably by repetitive central vagal stimulation. The effect is a generalized one, that is, cortical areas which have not previously been shown to receive specific projection paths from the vagal nuclei [Bailey & Bremer (19)] are affected. These authors suggested that the mediating mechanism resides in the ascending reticular system [Moruzzi & Magoun (20)].

Gellhorn (21) has also demonstrated the dual control of the cortical activity by increasing the depth of barbiturate anesthesia or the concentration of CO_2 in the inspired air, in which case the hypothalamic-cortical discharges are greatly affected and the optic or acoustic projection areas are only slightly, or not at all, depressed. In spite of this independence of the two afferent systems, it is suggested that perception is the result of their interaction in the sensory projection areas. In other words, the response of a sensory area, such as the auditory cortex, to an afferent stimulus will not be perceived unless the sensory projection area concurrently receives impulses from the hypothalamus to an adequate degree. In a *Victor Horsley Memorial Lecture*, Cairns (22) also stressed the fact that while in Horsley's time, consciousness was generally held to be a function of the cerebral cortex, the importance of brain stem and diencephalic mechanism as a basis for consciousness can not be overemphasized. In a review by Dell (23), the two afferent systems, one specific and one general through the brain stem mechanism and collaterals, are emphasized. It is the interplay of these two systems that establishes the functional unity of the central nervous system.

Autonomic drugs.—According to Tower & Elliott (24), the activity of the acetylcholine system (total acetylcholine content, cholinesterase) per unit weight is uniform in different samples of cerebral cortex. Similar analyses including other portions of the central nervous system were made by Burgen & Chipman (25), but the amounts vary widely in different regions of the brain. Chusid & Gutiérrez-Mahoney (26) revealed that topical application to the human cerebral cortex of acetylcholine chloride in high concentration induces recurrent, single high amplitude negative waves, followed by groups of negative waves or spikes. With small doses of atropine, lethargy is produced while larger doses result in hyperpnea and apparent excitement with motor restlessness followed by weakness and hypnosis [Meyers & Abreu (27)]. According to McIlwain (28), atropine is effective in inhibiting the increase in respiration and glycolysis of separate portions of cerebral cortex brought about *in vitro* by stimulation.

By measuring the percentage of inhibited cholinesterase in the nervous tissue of dogs with TEPP[2] and PPS[3], Burgen & Chipman (29) assumed that there are probably three possible arrangements of synaptic cholinesterase: (*a*) at the neuromuscular junction, postsynaptic and outwardly directed; (*b*) at sympathetic ganglia, presynaptic and outwardly directed; and (*c*) at the central synapses, presynaptic and inwardly directed. Data presented by Stewart (30) showed that lethal doses of TEPP increases the total acetylcholine content of brains of rats and under such conditions, free acetyl-

choline appears in the blood. The importance of the acetylcholine system in central nervous function has been reviewed by Hughes & Robinson (31).

Diencephalon

Hypothalamus.—Auer (32) has made a careful study of the cellular differentiation in the hypothalamus of the hamster during its postnatal stage in an attempt to correlate it with the functional development and localization. Stimulation of the hypothalamus from the anterior border of the supraoptic area to the level of mammillary bodies in the cat yields increased blood flow to the skinned limb (skeletal muscles), which, according to Eliasson *et al.* (33), is due to activation of sympathetic cholinergic vasodilator fibers. These authors used this observation to support their belief that there is no functional separation of the hypothalamus into anterior "parasympathetic" and a posterior sympathetic region. In a more recent article, Folkow & Gernandt (34) showed that in the cat, dilatation of the muscular vessels following hypothalamic stimulation is associated with a concomitant increase of electrical activity of the efferent nerve supply of the muscles. Sympathetic denervation eliminates both the nervous discharge and the dilator response. Meyer & Hunter (35) reported that in the cat, lesions in the region of the mammillary bodies and the inferior portion of the mammillo-thalamic tract produce symptoms of catalepsy and unresponsiveness.

Anand & Brobeck (36, 37) confirmed that increased food intake (hyperphagia and obesity) in rats and cats results from chronic bilateral destruction in the vicinity of the ventromedial nuclei of the hypothalamus, and extended their observation that bilateral lesions placed in the lateral hypothalamic area at the same rostrocaudal plane as the central part of the ventromedial nucleus make the animals refuse to eat. Even in animals previously made hyperphagic by medial lesions, eating ceases when the lateral areas are destroyed bilaterally. It is therefore assumed that the lateral areas contain a "feeding center" responsible for the central hunger reaction or the urge to eat, while the more medial region may be capable of exerting normally an inhibitory control over the feeding desire. In this connection, McFadzean (38) reported a case of meningoencephalitis complicating antirabies vaccination in whom narcolepsy-obesity syndrome is presented, suggesting hypothalamic disturbance.

The late Professor Bazett (39) formulated an interesting theory of reflex controls for the regulation of body temperature at rest and during exercise. Besides the established superficial receptors for heat and cold (Ruffini's and Krause's, respectively), the author assumed that a second set of heat receptors lies deeper at the level of the subcutaneous junction. The former receptors are concerned with vascular readjustments induced by external heat; the deeper heat receptors are concerned with sweating and are stimulated readily by internally produced heat. Forster & Ferguson (40) demonstrated in the cat that the vasomotor state, as indicated by ear temperature, is clearly unrelated to hypothalamic temperature changes

and concluded that vasomotor thermoregulation is under reflex control. On the other hand, heat polypnea and panting do not occur until the hypothalamic temperature has risen above the control range and, together with other evidence, these authors concluded that the respiratory heat loss mechanism is primarily under central or hypothalamic control.

Hypothalamo-hypophysial system.—Stimulation of the anterior hypothalamus in the vicinity of the supraoptic nucleus was shown by Andersson (41) to induce milk ejection in the lactating sheep and goats. Andersson (42, 43) showed further that the mechanism is mediated by the neurohypophysis since (*a*) the response is unaffected by denervation of the udder; (*b*) blood, taken from the jugular vein of an animal stimulated in the supraoptic region, increases the milk flow when injected intravenously into another lactating animal; and (*c*) a small dose of Pitocin (the oxytocic principle) also causes an ejection of milk in lactating goats. The author pointed out that other procedures known to release the posterior lobe hormone such as intracarotid injection of hypertonic saline solution, or stimulation of the central vagus, also induce a definite milk flow. In this connection, Baez *et al.* (44) showed that ferritin-induced oliguria is also related to the stimulation of the neurohypophysis, with the release of antidiuretic principles. Evidence favorable to this concept is as follows: (*a*) antidiuresis is induced by much smaller amounts of ferritin injected into the carotid artery than are required by the intravenous route; (*b*) urine excreted during ferritin-induced oliguria contains a Pitressin-like antidiuretic substance; and (*c*) pituitary stalk resection abolishes the antidiuretic effect of ferritin. The inhibition of the rate of urine flow can also be produced by a far smaller dose of acetylcholine injected into the carotid artery than into the vein of an unanesthetized, atropinized dog [Pickford & Watt (45)]. This observation corroborates the previous work that acetylcholine releases the antidiuretic hormone by a central action. If epinephrine is given at the same time or before the injection of acetylcholine, the normal inhibition of renal activity may be prevented [Duke & Pickford (46)]. These authors suggested the possibility that the epinephrine interacts with acetylcholine in the central nervous system, possibly at the supraoptic nuclei. Duke *et al.* (47) also investigated the site and mechanism of the antidiuretic action of morphine. Decreased urine excretion is produced by morphine given intravenously to the unanesthetized dog or injected into the supraoptic nuclei under chloralose anesthesia. This response is unaffected by previous injection of DFP[2] into the supraoptic nuclei of the unanesthetized dog, but abolished by section of the supraoptic tracts. These authors concluded that morphine induces antidiuresis by a direct effect on the supraoptic cells, causing the release of the antidiuretic hormone of the posterior lobe of the hypophysis without the intervention of the acetylcholine-cholinesterase system.

Bodian (48) has further enlightened the close interrelationship between the hypothalamus and neurohypophysis in the opossum by demonstrating histologically the mode of termination of nerve fibers in the palisade zone,

with their dense envelopment of neurosecretory substance. The morphologic relation appears to be adapted to bring these elements into close contact with the blood vessels of the septal layer.

It was shown by Sawyer *et al.* (49) that Banthine (β-diethylaminoethyl xanthine-9-carboxylate methobromide) is effective in blocking copulation-induced ovulation in the rabbit if injected within a few seconds post-coitum, thus strengthening the concept of a cholinergic component in the anterior pituitary activating mechanism. Porter (50) reported that in cats and monkeys a marked increase in electrical activity, limited to the posterior hypothalamus, is induced by epinephrine and other stimuli, such as insulin and hypoxia. These results provide added support for participation of the posterior hypothalamus in the pituitary-adrenal response to stress.

Thalamus.—The controversy concerning the existence of a sleep center or a waking center in the hypothalamus has been clarified. The exact location of a sleep center proclaimed by Hess (51) has not been definitely known to other investigators, until Hess presented his work in considerable anatomical detail in 1947 (52). The region that produces sleep on stimulation in cats is identified as the massa intermedia of the thalamus. Recently, Hess, Jr. and his collaborators (53) confirmed this and showed that slow frequency stimulation of the medial portion of the thalamus produces not only a behavior pattern identical to that of natural sleep, but also large spindles in the cortical electroencephalograph characteristic of sleep. The latter has been reported as the recruiting response by Dempsey & Morison (54), and the thalamic area initiating such responses has been carefully mapped out by Starzl *et al.* (55, 56). Although there is slight overlapping between it and the areas containing the ascending pathway for the activating reticular system [Starzl *et al.* (57)], in general, the former occupies the dorsomedial portion of the thalamus, and the latter, the ventral and somewhat lateral position. In a recent article on sleep, Bremer (58) interpreted the sleep characteristics exhibited in "cerveau isolé" as mainly due to exclusion of bulbo-mesencephalic activating reticular system of Moruzzi & Magoun (20), and assumed that a diencephalic sleep mechanism may not be necessary. However, since EEG spindles are seen not infrequently in "encéphale isolé" cats in which the activating reticular system is intact, sleep still appears to be a complex physiological phenomenon, involving an interaction of a subcortical waking and sleep mechanism and the cortex.

According to Meyer & Hunter (35) and Schreiner *et al.* (59), akinetic and apathetic states may be observed in cats with lesions in the anteromedial thalamus, and reactivity to noxious stimuli is markedly increased (59). On the other hand, Baird *et al.* (60) observed that in unanesthetized cats stimulation of the anterior thalamic nucleus produces a "reaction of alertness," and bilateral lesions produce a brief state of catalepsy followed by a transient period of reduced reactivity to painful stimuli. These authors also observed slowing or arrest of respiration in anesthetized cats and schizophrenic patients, and, not infrequently, a fall in blood pressure in

cats, when the anterior nucleus is stimulated at a frequency of 30 per sec. The inhibitory respiratory effects, though similar to those obtained on stimulating the cingular gyrus, are unrelated to the centrifugal paths originating from the cortical area, because the reaction persists in cats after either of the structures is destroyed surgically.

Brain Stem

Activating reticular system.—A wealth of information has been gathered by Magoun and his collaborators on the activating reticular system in the rostral portion of the brain stem (20, 57, 61 to 64). The same system normally functions in the descending as well as in the ascending directions: to subserve on one hand, the behavioral facility (65), and on the other, the central alertness that characterizes the waking state. A rich supply of collateral connections to the midbrain tegmentum, sub- and hypothalamus, and ventromedial thalamus is encountered. These findings offer an explanation for a number of the generalized consequences of afferent stimulation which have been difficult to understand in terms of conduction within classical sensory paths. Specifically, they suggest that the arousing and awaking influences of sensory stimulation are effected subcortically by collateral excitation of the reticular activating system in the brain stem. To this reviewer, it is not yet clear how this mesencephalic awaking mechanism is integrated with the waking center in the posterior hypothalamus previously reported by Harrison (66). Since extensive connections are known to exist between the two structures, it is possible that the arousal reaction produced by hypothalamic stimulation is accounted for by activation of the ascending paths of the mesencephalic mechanism. However, the possibility is not excluded that the hypothalamic awaking reaction is effected through a separate, indirect or descending, mechanism. In connection with the mesencephalic awaking mechanism, it is interesting to note that Kaplan *et al.* (67) observed marked stupor in a patient with hemorrhagic lesions in the midbrain.

Respiratory control and reflexes.—Tang & Ruch (68) localized the pneumotaxic center in the cat to the dorsal half of the anterior pons. Ngai & Wang (69) stimulated the dorsolateral reticular formation of the rostral pons and produced an accelerated respiration. In the vagotomized cat, bilateral destruction of the responsive region transforms eupneic to apneustic respiration. They concluded that the pneumotaxic center resides in the dorsolateral portion of the rostral pontile tegmentum, stimulation of which yields a faster breathing. According to Johnson & Russell (70), the locus coeruleus is the classical pneumotaxic center. With both stimulation and ablation experiments in the cat, Ngai and others (71, 72) showed further that the apneustic pattern of respiration originates in the pontile mechanism, rather than one localized in the medulla. The residual respiratory activity in the medullary animal consists of periodic gasping, whether or not the vagi are intact. Therefore, the inspiratory center in the medulla is not continuously tonically ac-

tive as previously assumed. Hukuhara *et al.* (73) also observed gasping respiration in medullary rabbits. If, however, the pontile structures were left intact, apneusis occurs but only lasts for a short time. They therefore regarded this latter type of respiration as the result of the transient stimulating effect of the transection. In this reviewer's opinion, Hukuhara's interpretation cannot be correct, since apneusis or inspiratory cramp appears only after bilateral vagotomy and especially in cats, may last for many hours. Clinical cases with large bilateral pontile lesions showed a severe type of respiratory disturbance characterized by slow, labored, gasping or apneustic respiration [Steegmann (74)].

Amoroso *et al.* (75) recorded the action potentials of the respiratory neurones in the medulla of rats, cats, and dogs, and found that there is no definite separation into inspiratory and expiratory regions. Inspiratory discharges, however, tend to be concentrated in the caudal, ventromedial reticular formation of the rhombocephalon. More recently, Amoroso *et al.* (76) stimulated the medulla of sheep, and found that the loci for the production of maximal inspiratory and expiratory apneas are separable into clearly defined regions: (*a*) an inspiratory region which occupies a blunt, wedge-shaped volume of the ventromedial reticular formation, the base of the wedge being at the obex and the truncated end extending to the cephalad margin of the inferior olive; (*b*) an expiratory region which covers a larger extent than the inspiratory region and lies dorsal, anterior, and lateral to it. This is essentially in confirmation of what has been reported in the cat by Pitts *et al.* (77) and in the monkey by Beaton & Magoun (78).

Hoff & Breckenridge (79) have classified the basic respiratory patterns into three types, namely; panting, eupnea, and sighing; the last two are observed in medullary preparations. The sighing type of respiration is enhanced by vagotomy or morphine administration [Breckenridge & Hoff, (80)]. Additional information has been supplied about the complex role of vagus on the regulation of respiration (81 to 84). According to Bozler & Burch (81), the pulmonary vagal fibers are chiefly excitatory on inspiration, since the effects of vagal block, especially in dogs with an open chest, are slowing of inspiration and rate of respiration. Takagi *et al.* (82) claimed in the rabbit, cat, and dog that, in addition to the static inhibitory and static facilitatory fibers in the vagus, there is a third group of fibers for phasic facilitatory function which do not work during quiet respiration. Calma (83) reported that in cats a single shock applied to the central end of the vagus during inspiration causes the appearance of a motor discharge in the phrenic nerve, followed by a period of inhibition. With multiple shocks at a frequency of 10 to 20 per sec., the initial excitatory phase disappears and the phases of subnormality merge into one another, resulting in a prolonged inhibition. Culver & Rahn (84) attributed the ventilatory stimulation by chest compression in the dog to the action of the afferent vagus.

Cardiovascular control and reflexes.—Direct stimulation of the depressor area of the vasomotor central complex in the medulla oblongata of the dog

has revealed a marked vasodilatation of the hind limb which is abolished by appropriate sympathectomy or intra-arterial injection of Hydergin, an adrenergic blocking compound related to ergotoxine, but is unaffected by atropinization [Frumin *et al.* (85, 86)]. Similarly, the vasodilatation following stimulation of the carotid sinus or aortic depressor nerve is effected solely by an inhibition of the sympathetic constrictor tone [Frumin *et al.* (86); Celander & Folkow (87)]. Bernthal & Woodcock (88) showed that, when dogs deprived of carotid and aortic chemoreceptors are exposeed to hypoxia, small residual changes of blood flow occur in a limb separately perfused and connected to the body only by its nerves. Since the blood flow changes are not always in the same direction, it is suggested that oxygen deficiency simultaneously exerts two separate and opposite influences upon vasomotor neurons, one excitatory and the other depressant; and that the activity of the center at any stage of hypoxia reflects the algebraic sum of these opposing influences. Kenfield *et al.* (89) studied the effect of renal substances on the central control of blood pressure and respiration in cross circulation experiments on dogs and found that the central control was unaffected. Bouckaert & Leusen (90) reported that the stimulating effect of CO_2 on the vasomotor system is minimal if the chemoreceptor reflexes are eliminated.

Rosenfeld & Drury (91) reported persistent hypertension in rabbits after occlusion of the carotid supply to the brain by ligating the internal, external, and occipital arteries distal to the sinus. Evidence is presented to show that the carotid sinus does not appear to be a factor in production of this hypertension [Rosenfeld (92)]. Rodbard & Saiki (93) demonstrated a marked hypertensive effect in the chick when the intracranial pressure is raised. These investigators suggested that the pressor response is not attributable to anoxia, because (*a*) only a small pressor response is observed when the chick is subjected to asphyxia or anoxia; (*b*) a marked pressor response is initiated almost instantly with momentary increase of intracranial pressure; and (*c*) an occasional depressor response is observed following a reduction in the intracranial pressure. They hypothesized an intracranial baroceptor similar to that of the carotid sinus, but did not indicate the possible location of the baroceptors. To this reviewer, it appears possible that the vasomotor center itself is sensitive to pressure changes.

Kaindl & Euler (94) showed that occlusion of both common carotid arteries increases the norepinephrine and epinephrine output from the suprarenal gland of the vagotomized cat. Daly & Schweitzer (95, 96) reported bronchodilatation in dogs and cats following a drastic fall in the carotid sinus and aortic arch pressure by hemorrhage, and constriction when the pressure is raised by transfusion of the same blood or when the carotid sinus nerve is stimulated. This bronchomotor response is not affected significantly by section of the sympathetic innervation of the lungs, but is appreciably reduced by vagotomy or atropinization. Nevertheless, a considerable "residual effect" exists after all autonomic innervation is eliminated. These authors concluded that the bronchomotor effect is elicitable

reflexly by changing markedly the baroceptor activities in the carotid sinus and the aortic arch, and the efferent limb of this reflex arc is mainly vagal. According to Scott & Reed (97), the integrated changes in P amplitude, P-R and R-R intervals of the electrocardiogram in response to carotid sinus compression in dogs and cats are due primarily to vagal impulses, and are independent of the sympathetic innervation. Kenny *et al.* (98) reported no consistent change in the cardiac output, as measured by Fick's principle, following carotid sinus stimulation in vagotomized as well as nonvagotomized dogs.

Local administration of epinephrine in the wall of the carotid sinus has been observed to cause a fall in the systemic blood pressure. Heymans & Heuvel-Heymans (99) postulated that epinephrine causes stimulation of the baroceptors by local contraction of the sinus wall, while Palme (100) claimed a direct stimulating action of epinephrine on receptors in the carotid sinus region. According to Mazzella *et al.* (101), systemic hypotension is still elicitable in the dog by local injection of epinephrine in the carotid sinus wall when the chemoreceptors have been differentially eliminated. Landgren *et al.* (102) made action potential studies in both cats and dogs and reported a definite increase in the baroceptor impulse traffic when epinephrine is applied locally to the carotid sinus. These investigators did not feel justified in making any definite pronouncement on the excitation mechanism of the carotid baroceptors. But the marked reduction of the baroceptor activity reported by them when sodium nitrate (a muscle relaxant without any local anesthetic action on the nerve endings) is administered locally, appears to this reviewer to be in favor of the theory that changes in the intramural tension of the sinus wall stimulate the baroceptors.[4] According to Witzleb (104), both the baroceptors and chemoreceptors in the carotid sinus are sensitive to temperature changes, since he found that in cats small temperature changes of the blood in the common carotid artery call forth changes in impulse frequency in the sinus nerve. He could not demonstrate specific heat-sensitive receptors with a mechanism of action similar to the thermoreceptors in the tongue.

Jewell (105) has made a careful study of the anastomotic branches of the internal and external carotid circulation by injecting colored gelatin masses into the cerebral vessels in the dog, and has described five anastomoses: the occipital-vertebral, the ascending pharyngeal-internal carotid, and those between the internal maxillary artery and three intracranial vessels—the anastomotic, the ophthalmic, and the ethmoidal arteries. Of these anastomoses, the occipital-vertebral and the internal maxillary-anastomotic communications are considered to be important routes by which carotid blood might reach the brain. Both Chungcharoen *et al.* (106) and Wang *et al.* (107, 108) observed in the dog that there is considerable back-

[4] In an abstract article (103) which appeared in the *Journal of Physiology (London)*, these authors, presumably upon the basis of the same data, concluded that their electrical studies support the interpretation given by the Heymans.

flow into the sinus region when the common carotid arteries are occluded. However, they disagree on the relative importance of the contribution of the occipital-vertebral anastomosis as the backflow channel. The latter group presented clearcut evidence that the external carotid arteries are the main channels for drainage and the occipital arteries for back flow when an appreciable pressure differential exists between the sinus region and the systemic arterial circulation, particularly the vertebral arteries. Under certain conditions, the back flow is so marked that the intrasinual pressure rises to within a few millimeters of the preocclusion level, yet the systemic hypertension following carotid occlusion is maintained at the same level. These results suggest that the carotid sinus pressor response is not entirely dependent upon the extent or the duration of the reduced intrasinual pressure.

Youmans *et al.* (109) demonstrated that sectioning of the aortic arch and carotid sinus nerves does not completely abolish the cardio-inhibitory response elicited in the unanesthetized rabbits following administration of the pressor compounds, Pitressin (Vasopressin Injection, USP) and Neosynephrine (phenylephrine hydrochloride). These authors attributed the residual cardio-inhibitory response to the presence of varying numbers of depressor fibers in the vagus trunks which remain intact. Pitressin also produces a considerable decrease or even suspension of the tonic cardio-accelerator activity in unanesthetized dogs in which the vagi are sectioned at a high cervical level and the carotid sinus excised [Youmans *et al.* (110)]. The site of this inhibitory action is not clearly established but these investigators ruled out all afferent influences from structures below the level of the diaphragm.

Landgren & Neil (111, 112) have renewed the investigation on the contribution of carotid chemoreceptor mechanism to the rise of blood pressure caused by carotid occlusion or hemorrhage, and reported that chemoreceptors play an important role in the two procedures. They further showed (113) that it is possible to stimulate the chemoreceptors alone by local application of sodium cyanide, lobeline, and sodium citrate without simultaneously affecting the baroceptors. Under such conditions, these compounds cause a small but definite reflex rise in blood pressure and increase in heart rate. Liljestrand (114) found that local application of eserine to the carotid bodies increases the vasomotor and respiratory responses to oxygen deficiency and carbon dioxide accumulation. On the other hand, the sensitivity of the chemoreceptors to these stimuli is diminished or abolished by local treatment with atropine, whereas clamping of the common carotid arteries induces the typical rise in blood pressure. The author interpreted these results as evidence that acetylcholine is the chemical mediator within the carotid body.

The hypotensive action of veratrum alkaloids has been extensively investigated. Richardson *et al.* (115) observed that veratrum alkaloids produce a reversible blockade of the carotid sinus pressor reflex in the dog, and suggested that an important action of the alkaloids may be directly on the

vasomotor center. Gruhzit & Moe (116) suggested that the hypotensive action of Veriloid[5] is due in considerable measure to stimulation of the carotid sinus pressoreceptors, since Veriloid no longer produces a fall in blood pressure in dogs deprived of the pressoreceptors. However, Jarisch *et al.* (117) observed in the cat that, although intracarotid injection of 10 to 40 μg of veratrine leads to stimulation of both chemoreceptors and baroceptors, the intravenous administration of 50 to 100 μg of veratrine does not change either chemoreceptor or baroceptor activity. It therefore appears that the carotid baroceptors do do not contribute to the arterial hypotension elicited by intravenous administration of veratrine in even relatively large doses. Swiss & Maison (118) also found that in cross circulation experiments in the dog such hypotension is not decreased by carotid denervation. Borison & Fairbanks (119) claimed that in the cat the nodose ganglion is the receptor site of the vasodepressor action of Veriloid.

Central vomiting mechanism and motion sickness.—Wang & Borison (120) have previously revealed a trigger zone in the area postrema, ablation of which produces, in chronic preparations, permanent refractoriness to apomorphine emesis. These dogs still vomit after a threshold dose of oral copper sulfate, which indicates that the vomiting center is intact. In a recent article by Wang & Borison (121), the location of the vomiting center is further confirmed to be in the dorsolateral reticular formation of the medulla oblongata. In this investigation, slowly progressive lesions are made by radon seed implantation in the reticular formation without injury to the periventricular gray matter. Dogs with such discrete lesions placed bilaterally show no response to apomorphine and are also refractory to large doses of copper sulfate given via the gastric route.

The emetic trigger zone is also concerned with the mediation of vestibular impulses in motion sickness. According to Wang & Chinn (122), dogs which are sensitive to swinging movements on several successive trials, become consistently resistant to motion for many months subsequent to ablation of the trigger zone. They suggested that the vestibular impulses elicited by motion traverse the nodulus and uvula of the cerebellum [Bard *et al.* (123)] and the trigger zone, and finally reach the medullary vomiting center.

Swiss (124) showed that dogs vomit after intragastric Veriloid[5] whether or not the stomach is denervated. They suggested that Veriloid acts directly on the vomiting center. Borison & Fairbanks (119) reported that the emetic response in cats to Veriloid is not affected by vagotomy, but is completely abolished after excision of the nodose ganglion. They concluded that the nodose ganglion is the site of emetic action of Veriloid.

Spinal Cord and Peripheral Visceral Afferents

Earle (125) has made degeneration studies of the spinal cord in the cat, and confirmed the fact that Lissauer's tract consists of numerous short fibers of not more than one or two spinal segments. There is no evidence

[5] Veriloid is the trade name of a mixture of ester alkaloids of *Veratrum viride.*

for any long fibers to support the idea of a direct, uninterrupted, either endogenous or exogenous, pain pathway within this tract. The author suggested that a polysynaptic pathway may exist. The spinal pathways for visceral afferents have been investigated with the "evoked potential technic" by Amassian (14) and Aidar *et al.* (16), as previously cited.

Clinical evidence concerning the location within the human spinal cord of the centripetal pathways from the bladder and urethra have been presented by Nathan and Smith (126). According to them, the spinothalamic tract subserves the sensation of a full bladder initiating the desire to micturate, the sensation of pain from the bladder and urethra, and the sensation of temperature from the urethra. That subserving touch and pressure from the urethra lies within the posterior column. Howet (127) reported that in the rabbit with bowel obstruction, crushing the thoraco-lumbar spinal cord changes the color of the dilated intestine from that of cyanosis to bright red, and improves the gut function as well as the general symptoms. The author suggested that in advanced intestinal obstruction, a vasoconstrictor reflex contributes to the anoxia of the bowel which aggravates the condition of the animal.

In order to investigate the distribution of visceral afferent nerves in the mesenteric region, Downman (128) pinched the small intestine of cats, and used pupillary dilatation and arterial pressure changes as reflex indices for the passage of afferent impulses into the spinal cord. He found that the mesenteric nerve fibers (afferent, vasoconstrictor, and inhibitory) run up or down the intestine before branching to innervate a segment of intestine not more than 2 cm. long. There is a slight overlapping between adjacent nerve bundles up to 20 per cent of the length of each territory.

An operation for the successful relief of pain in angina pectoris has been reported by Robson (129). It consists of a resection of the second to the fifth thoracic sympathetic ganglia and an extra spinal section of the first thoracic posterior root with careful preservation of the stellate ganglia. Rinzler (130) has discussed the mechanisms of production of cardiac pain and various therapeutic measures. According to Pearce & Whitteridge (131), there is a good correlation between vagal fiber activities and pulmonary arterial pulse pressure in the dog. Therefore, they suggested that the so-called pulmonary vascular fibers arise from endings in the pulmonary circuit, and their function is for vascular adjustments. Morton *et al.* (132) reported that unilateral vagus section just below the recurrent laryngeal nerve in patients with bronchogenic carcinoma usually abolishes pain of bronchial origin on the homolateral side.

Lynn & Simeone (133) were not able to demonstrate reflex circulatory changes in the contralateral limb of the dog by intense stimulation of the vessels by chemical and electric means as previously reported by Freeman *et al.* (134). On the other hand, similar painful stimuli applied to a sensory nerve or to the neighboring perivascular tissues in the same animal yield contralateral vasomotor reflexes which are unaffected by homolateral sympa-

thectomy. They concluded that painful impulses from the limbs are carried centrally by afferent fibers in the cerebrospinal nerves and not by afferent fibers in the sympathetic chain. According to Christensen *et al.* (135), there is an extensive nerve plexus along the entire length of the vertebral artery of the cat, in which the fibers are mainly unmyelinated and probably sensory in function.

Peripheral Visceral Efferent System—Cranio-Sacral Outflow

Parasympathetic stimulation.—Data reported by Hoffman *et al.* (136) showed that vagal stimulation has no effect on the excitability or conduction velocity of the dog's ventricle. On the other hand, strong vagal activity increases the atrial diastolic conduction velocity without any measurable change in the latency of response. The duration of the absolute refractory period of the atrium is regularly decreased, and the thresholds during the relative refractory period are lowered. Vagal stimulation also increases the vulnerability of the atrium to fibrillation from single shocks; this is demonstrated by an increase in the duration of the vulnerable period and a fall in fibrillation thresholds. The role of vagus in the circulatory system has been studied by Okinaka *et al.* (137, 138); of particular interest is the evidence for the cardio-accelerator fibers in the vagus nerve. These investigators are able to eliminate the cardio-inhibitory fibers in the vagus by making a chronic section of all the myelencephalic rootlets of the accessory nerve.

Using a perfused lung of the dog, Daly & Hebb (139) showed that, in the absence of atropine, stimulation of the vagosympathetic trunk yields vasodilatation, whereas with atropine, vasoconstriction occurs. This latter response is potentiated by cocaine and suppressed or reversed by ergotoxine. These authors attempted to identify the origin of the pulmonary vasomotor fibers without much success. Both types of fibers survive degenerative resection of the vagosympathetic trunk at the cricoid cartilage level, thus indicating that, at least a large proportion of these fibers are not derived from the cranial nuclei, the superior cervical ganglion or the nodose ganglion, but in all probability, from the upper thoracic sympathetic outflow.

The experimental data reported by Dreiling *et al.* (140) revealed that, in man, vagal stimulation induced by insulin hypoglycemia produces a pancreatic fluid in which the total volume is low and the amylase is high as compared with the response to secretin. On the other hand, the bicarbonate concentration is not augmented. The main effect of stimulation, then, is a marked increase in enzyme secretion.

Parasympathetic denervation.—Antia *et al.* (141) obtained the following effects in the stomach of the dog after bilateral transthoracic vagotomy: (*a*) The appearance of free HCl in the secretion under basal conditions occurs with the same frequency as before vagotomy but at a diminished rate. (*b*) The acid-secretion response to insulin hypoglycemia is abolished in all animals and no return of response is observed even after one year. (*c*) The

response to a standard dose of histamine is, on the average, decreased by about 30 per cent. However, the depression following vagotomy is due to a decreased sensitivity to stimulation rather than a depressed secretory capacity. (*d*) The changes in acid concentration are, in general, parallel to the changes in total acid output. The greatest depression of acid secretion occurs at the six-month postvagotomy examination period. (*e*) The emptying of a liquid meal occurs more rapidly after vagotomy. However, the addition of fat to the meal still causes as great a delay in emptying after as before vagotomy. In this respect, it is interesting to note that Quigley & Louckes (142) made extensive observations of the pyloric sphincter tone and motility in dogs before and after vagotomy, and found no permanent change in behavior of the sphincter following vagotomy.

Lewis (143) also reported that after section of vagus nerves to total-stomach pouches in the dog, there is a profound decrease in the acid output during basal conditions and the secretory response to various stimuli is reduced. Storer *et al.* (144), on the other hand, observed a marked increase of acid secretion from Heidenhain pouches in the dog following section of the vagus nerves to the main stomach. This is explained by the fact that food remains in the stomach for a longer period after vagus section than before, thereby increasing the secretion in the pouch during the gastric phase.

According to Jefferson *et al.* (145) and Necheles & Jefferson (146), high section of both vagi in the dog, just below the pulmonary hilus, produces cardiospasm, which is absent if the left phrenic nerve is also sectioned. They attribute the beneficial effect of the left phrenicotomy to the fact that the stomach is thus raised and the axis between cardia and pylorus is straightened out.

Thistlethwaite (147) reported that following vagotomy or Banthine administration in dogs, the volume and amylase content of pancreatic secretion are reduced. In vagotomized patients, insulin hypoglycemia does not stimulate pancreatic secretion at all as it does in those with intact vagi [Dreiling *et al.* (140)]. But the pancreatic response to secretin in such patients is entirely normal. Bingham *et al.* (148) reported that in patients with duodenal ulcers and essential hypertension, bilateral transthoracic vagectomy and extensive thoracic sympathectomy produce predominantly a vagectomy "effect," with gastric hypomotility. These patients experience no loss of sensations of appetite, hunger, nausea, and gastrocolic reflex.

Kuntz (149) has made studies on the origin and early development of the pelvic neural plexus in pig embryos, and reported that the ganglion cells in the plexuses are derived largely from sacral segments of the central nervous system via the pelvic nerves and also from thoraco-lumbar segments via the hypogastric plexus. Schlitt *et al.* (150) extirpated bilaterally the hypogastric nerves and the inferior hypogastric or Frakenhauser's ganglia (pelvic autonomic neurectomy) in patients with ulcerative colitis with a good therapeutic response.

Carpenter & Root (151) compared the pressure-volume curves of feline

bladder in which nervous conduction has been blocked with epidural procaine with those obtained several weeks after bilateral section of the sacral roots, and demonstrated that with the latter procedure the bladder can accommodate a larger volume of fluid at a given intravesical pressure than with the former. These denervated organs empty only by overflow incontinence and some residual urine is always present. The animals with only the pelvic nerves sectioned do not exhibit overflow incontinence, because the pudic nerves which innervate the external sphincter remain intact. The tonically contracted sphincter holds back large quantities of urine which are periodically voided in small amounts. The bladders so denervated show hyperplasia and thickening of all components of the muscular layer [Carpenter (152)].

Emmelin *et al.* (153, 154) produced supersensitivity in the submaxillary gland of the cat to various chemical stimuli by one of the following procedures: (*a*) surgical section of chorda tympani, (*b*) chronic treatment with atropine, (*c*) superior cervical ganglionectomy, and (*d*) administration of cocaine. A common feature in all these cases is that sensitization is nonspecific. But the submaxillary glands following the first two procedures show maximum sensitivity to epinephrine, and microscopically only scattered demilunes devoid of secretory granules are seen. Emmelin (155) has also reviewed the different theories of paralytic secretion, and indicated that secretion is not the result of a spontaneous activity but is due to the supersensitivity of the denervated glands to epinephrine. In other words, paralytic secretion, according to Emmelin, belongs to the same group of phenomena, as paradoxical pupillary dilatation and the pseudomotor contractures of Philipeaux and Vulpian.

Chemical mediators.—Anand (156) reported that stimulation of the vagus nerve produces a more marked inhibitory effect on the frog heart when the temperature of the heart is high than when it is low. Fluid withdrawn from the heart chambers after vagal stimulation at higher temperatures contains an increased amount of acetylcholine. The author concluded that the increased vagal inhibition observed at higher temperature is caused by increased liberation of acetylcholine.

Vasodilatation in skin following dorsal root stimulation ("antidromic vasodilatation") is due to liberation of a chemical transmitter at the peripheral ends of the sensory nerves,[6] but about the nature of the transmitter little is known. According to Ibrahim *et al.* (157), stimulation of the posterior root fibers in the dog increases the blood flow to the skin (but not to the muscles) of the hind limb with increased release of histamine. The response is prevented by antihistaminics (Antistine, Mepyramine, and Pyribenzamine).[7] It was concluded that the "antidromic vasodilatation" in the skin is

[6] Sensory fibers which transmit vasodilator impulses antidromically are not parasympathetic by definition.

[7] Antistine——2-phenyl-benzylaminomethyl-imidazoline hydrochloride; Mepyramine—2-[2-Dimethylaminoethyl(*p*-methoxybenzyl)-amino]pyridine; Pyribenzamine—2-[Benzyl(2-dimethylaminoethyl)amino]pyridine hydrochloride.

due to the release of histamine. On the other hand, Holton & Perry (158) stimulated the peripheral end of the cut great auricular nerve and obtained increased vascularity in the sympathetically denervated rabbit's ear. These authors suggested that "antidromic dilatation" is brought about by the liberation of a chemical transmitter; but the long latency and duration of the effect make it unlikely that the transmitter is either acetylcholine or histamine. The response is neither potentiated by eserine nor affected by the antihistaminic, Mepyramine. Holton & Holton (159) also extracted a dilator substance from both dorsal and ventral roots, which is not identical with acetylcholine, histamine, substance P, adenosine, bradykinin, or kallikrein. Erici & Uvnäs (160) demonstrated nerve fibers in the trigeminal part of the chorda-lingual nerve which are capable of transmitting vasodilator impulses to the tongue of cats. The response is not abolished by atropine.

Peripheral Visceral Efferent System-Thoraco-Lumbar Outflow

Sympathetic ganglia.—According to Gatenby & Moussa (161), "senility granules" are most noticeable in the sympathetic ganglia in a man 60 years old. They are some form of neurosecretion, originating in the Golgi apparatus, that have migrated to the axon hillock region. Nedzel (162) showed that the chromidial substance is definitely less in the sympathetic ganglia of hypertensive patients and also of dogs made hypertensive by renal ischemia. Additional data on the superior cervical ganglion of the cat are interpreted by Shaw *et al.* (163) to mean that this ganglion contains two types of cells; one type for vasoconstriction and another for vasodilatation. Eccles (164, 165) has studied synaptic transmission of isolated rabbit sympathetic ganglia and responses of curarized ganglia.

Sympathetic stimulation and sympathomimetic substances.—Investigation on the effect of epinephrine infusion (1 μg. to 20 μg. per min.) on the normal human heart has been carried out by Kjellberg *et al.* (166, 167), using electrokymography, phonocardiography, and electrocardiography. His data showed that epinephrine (*a*) increases the systolic pressure and lowers the diastolic pressure, thereby increasing the stroke volume; (*b*) accelerates the speed of ventricular contraction with a shortened isometric contraction phase; (*c*) usually increases the heart rate, and (*d*) increases the amplitude of the first and second heart sounds. Blocking of the vagus with methyl scopolamine nitrate has a similar effect except that the heart rate and the blood pressure are considerably more affected than the contraction of the heart. In isolated surviving pulmonary arteries and veins of man, swine, dog, and cat, Smith & Coxe (168) observed marked vasoconstriction following test doses of epinephrine (50 μg.) or *l*-norepinephrine. Changes in pulmonary resistance were also studied by Edwards (169) in a lobe of lung retaining its natural blood supply by simultaneous registration of pulmonary arterial pressures and rates of venous outflow. The author demonstrated a small but definite increase in resistance following injection of epinephrine (3 cc. of 1/50,000) directly into an artery of the lobe.

By means of serial angiography, Daniel & Prichard (170) showed that stimulation of the distal end of the divided hepatic nerve causes a constriction of intrahepatic vessels of the portal venous tree in the rat, rabbit, cat, dog, and monkey, with a marked rise in the portal pressure, and an accelerated transhepatic circulation. Intraportal administration of epinephrine causes similar effects on the intrahepatic portal circulation. Using the bromsulphalein and hepatic catherization technic, Bearn *et al.* (171) found that the estimated hepatic blood flow and splanchnic oxygen consumption are definitely increased in man following continuous intravenous administration of epinephrine at a rate of 0.1 μg. per kgm. per min. On the other hand, *l*-norepinephrine injected at a rate of 0.1 to 0.2 μg. per kgm. per min. causes a slight decrease in the estimated hepatic blood flow and a slight increase in splanchnic oxygen consumption. Likewise, King *et al.* (172) showed that *l*-epinephrine (average, 37 μg. per min.) produces an increased cerebral blood flow (nitrous oxide method) and cerebral oxygen consumption, with no significant change in cerebrovascular resistance. On the other hand, *l*-norepinephrine (average, 17 μg. per min.), causes a marked increase in cerebrovascular resistance, and a decrease in cerebral blood flow despite a substantial increase in mean arterial blood pressure. Cerebral oxygen consumption is not significantly altered.

The influences of sympathetic stimulation or sympathomimetic substances on renal hemodynamics and function have been studied by a number of investigators (173 to 181). Houck (173) stimulated electrically the left kidney artery nerves in the nembutalized dog while using the right kidney as control, and found that in the stimulated kidney, the urine flow, glomerular filtration rate (creatinine clearance) and renal blood flow (PAH^2 clearance) are depressed with a reduced tubular excretory (Tm_{PAH})[2] and reabsorptive (Tm_G)[2] capacities. There is no evidence by India ink injection of a Trueta shunt. According to Block *et al.* (174), stimulation of the renal nerves in the dog decreases the output of urine, creatinine and PAH clearances, and PAH extraction ratio, but the values return to practically normal levels within 1 to 2 hr. even though the stimulation is continuous. Vasoconstriction of the canine kidney is limited to the vessels of the cortex, including the juxtamedullary region [Block *et al.* (175)]. According to these investigators, blood remains static in the medullary vascular bed and significant shunting of blood from the cortex to the medulla is not observed. On the other hand, the Oxford group [Daniel *et al.* (176)] demonstrated convincingly with the angiographic or India ink injection technic that, following electrical stimulation of the renal nerves, severe hemorrhage and the intraaortic injection of epinephrine, an ischemia of the renal cortex with maintained circulation through the medulla occurs in the cat, dog, sheep, and monkey as well as in the rabbit. However, in the dog, these investigators noted that the cortex is not uniformly deprived of its circulation.

Comparable changes in renal hemodynamics and function were observed after intravenous administration of epinephrine in the dog [20 to 81 μg

per kgm., Houck (177); 0.07 to 1.4 μg per kgm. per min., Kaplan *et al.* (178)]. The latter group of investigators reported also a reduction in the concentration and excretion of Na and Cl in the urine. Like doses of *l*-norepinephrine produce only slight or inconstant alternations in GFR,[2] RPF,[2] and Na and Cl excretion. In trained conscious dogs, Pickford & Watt (179) reported that the rate of urine flow and the renal plasma flow (diodrast clearance) are decreased by epinephrine or norepinephrine (2 to 10 μg. per min.), while the glomerular filtration rate (creatinine clearance) is unchanged in the former and increased in the latter.

In man, Jacobson *et al.* (180) reported that a constant intravenous infusion of epinephrine in doses 10 to 18 μg. per min. causes a decreased glomerular filtration rate (inulin clearance), a decreased renal plasma flow (PAH clearance) and an increased filtration fraction. There is a decrease in the urinary excretion of sodium, chloride, and potassium, With graded infusions of *l*-norepinephrine (2 μg. to 18.3 μg. per min.) the glomerular filtration rate is unchanged but the renal blood flow is decreased [Pullman & McClure (181)]. There is no apparent effect on sodium or chloride excretion, but the potassium clearance is depressed. On the other hand, Smythe *et al.* (182) have compared the effects of epinephrine (USP), *l*-epinephrine, and *l*-norepinephrine. Despite a divergence in systemic hemodymanic activity of these substances, all excite a renal vasoconstriction which reduces renal blood flow without significant change in filtration rate. The urinary excretion of sodium and potassium is depressed. It is not easy to reconcile the differences in findings reported by the three groups of investigators, since they have employed the apparently identical methods upon healthy human subjects.

The problem as to whether, in man, the sweat glands receive an adrenergic as well as a cholinergic innervation has been investigated by Chalmers & Keele (183) and Sonnenschein *et al.* (184). They confirmed that intradermal injection of epinephrine or norepinephrine usually induces sweating in the skin of the forearm or the palm. The response is prevented by adrenergic blocking drugs and not by atropine, whereas spontaneous sweating (due to thermal changes or mental activity) is definitely cholinergic. These investigators concluded that even though human sweat glands respond to epinephrine or norepinephrine, the existence and function of an adrenergic innervation of these glands are not proven.

Sympathetic extirpation and ganglionic blocking substances.—McCubbin & Page (185) confirmed the previous contention that rapid heart rates and increased cardiac output are not the primary mechanisms in the maintenance of high blood pressure in dogs with chronic experimental hypertension due to buffer nerve section. These authors observed only slight decrease in systemic pressure following removal of the upper six thoracic sympathetic ganglia in neurogenic hypertensive dogs. They (186) also demonstrated that the hypotensive response to TEAC[2] in the neurogenic hypertensive dogs differs from that in the normotensive or renal hypertensive dogs. In the latter, TEAC fails to produce the severe fall in arterial pressure noted in neuro-

genic hypertensive animals and repeated doses are followed by decreasing hypotensive responses which soon become entirely pressor. In the neurogenic hypertensive dogs, the effect of repeated doses of TEAC is almost always depressor which, however, wears off in a few minutes. Some hypertensive patients have shown a response pattern to repeated injections of TEAC closely resembling that seen in experimental neurogenic hypertensive dogs. These authors demonstrated further that the TEAC hypotensive response pattern in neurogenic hypertensive dogs is not appreciably modified by sympathetic denervation of the heart or the adrenal glands; in fact, the pattern persists despite bilateral extirpation of the entire sympathetic chain except for the stellate ganglion. Brust *et al.* (187) also showed that in hypertensive patients TEAC produces an additional blood pressure fall when administered during high spinal anesthesia. Green (188) reported a good correlation between vasodilatation produced by thoracic or lumbar sympathectomy and that produced by tetraethylammonium in patients with peripheral vascular disease, and suggested the latter as a preoperative prognostic test in the operative relief for the vascular disorder.

According to Oberhelman *et al.* (189), division of the sympathetic nerve supply of the total stomach pouch in dogs with intact vagus nerves produces a significant increase in the quantity of 24-hour, gastric secretion. Such a sympathetic denervated pouch also yields increased secretion during insulin hypoglycemia or following histamine administration. Splanchnicotomy in the dog has been shown to affect the kidney to excrete an increased concentration of Na and Cl in the urine during mannitol diuresis [Kaplan *et al.* (190)].

Supersensitivity of various organs following sympathectomy has been a problem of interest to many investigators (191 to 194). Imig *et al.* (191) observed that the blood flow in the hind limb of the dog with chronic section of the sciatic nerve is increased following injection of epinephrine or norepinephrine in doses which are without effect in the normally innervated limb. Greenberg & Lambeth (192) showed that the chronic denervated dog heart is not consistently hypersensitive to epinephrine. These authors attributed the absence of supersensitivity of the denervated heart to the fact that the dog metabolizes epinephrine more rapidly than the cat. On the other hand, Innes & Kosterlitz (193) observed that chronic postganglionic sympathectomy potentiates the chronotropic action of norepinephrine, but not that of epinephrine even in the cat. According to Burn & Robinson (194), denervation of the nictitating membrane, the iris, and the blood vessels of the cat results in a fall in amine oxidase activity in all three tissues. These authors suggest that amine oxidase at the postganglionic adrenergic terminations plays a role similar to cholinesterase at cholinergic nerve endings and that the supersensitivity of the denervated structure is related to the decreased amine oxidase content. However, in the nictitating membrane the decrease in the enzyme content is greatest at 8 to 10 days after denervation and the amount returns to that of normal membrane by the thirty-third day. This

finding is not correlated with the supersensitivity of the membrane, which remains permanently. These investigators explained the discrepancy by assuming that the oxidase in the chronically denervated organ is located at an ineffective site. However, it appears difficult for this reviewer to accept this explanation because of the nonspecific nature of supersensitivity of the denervated structures.

Sympathetic mediators.—According to Fleetwood (195), patients during anxiety show an increased blood content of a sympathetic substance, which gives responses in the test organs similar to norepinephrine. Outschoorn & Vogt (196) also reported that stimulation of cardioaccelerator nerves in the dog causes the release of norepinephrine into the coronary blood. Euler & Purkhold (197) revealed that, in the sheep, sectioning of the periarterial nerves to the spleen, kidney, salivary glands, and liver is accompanied by a fall in both norepinephrine and epinephrine content in these organs. The former decreases after denervation more markedly than the latter. Vogt (198) found, however, that venous blood from the chronically denervated adrenal gland of the cat contains both norepinephrine and epinephrine in the same proportion as that in the normal cats at rest or following stimulation of the splanchnic nerves.

Erici *et al.* (199) demonstrated in the cat that the sympathetic nerves to the tongue contain both vasoconstrictor and vasodilator fibers. The latter are believed to be cholinergic. Folkow (200) presented data to show that stimulation of the lumbar sympathetic chain in the cat results in nearly maximal response for either vasoconstriction or vasodilatation when the rate of stimulation is only 6 to 8 per sec. If the stimulation rate exceeds 15 to 20 per sec., the vasomotor effect declines, suggesting damage of some of the stimulated fibers or an exhaustion of the mediator release mechanism. The author suggested that under physiological conditions the sympathetic fibers fire at rates seldom or never exceeding 6 to 8 impulses per sec. and at these discharge rates the adrenergic transmitter is mainly destroyed at the site of release, probably by an enzymatic process.

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SPECIAL SENSES: THERMAL RECEPTORS[1]

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In the chapter on heat and cold of the *Annual Review of Physiology* (1950), Hardy (1) summarizes his article by saying that although our knowledge of the central thermoregulatory mechanism principally located in the hypothalamus has become much clearer, much more information is needed about the temperature characteristics of the cells of the hypothalamus as well as about the sensations of heat and cold which arise in the skin.

In the last few years the functioning of the thermal receptors has been subjected to more objective investigations, the results of which give an en- entirely new view of the peripheral afferent part of the thermoregulatory system, as well as of many sensory phenomena hitherto the subject of much debate. For that reason it was considered justified to limit this review entirely to thermal receptors.

The temperature movements in the skin have been subject to theoretical as well as experimental investigations by Hensel (2, 3), who has developed effective methods for recording the intracutaneous temperature gradient in stationary conditions as well as a precision-flow-calorimeter for measuring the steady heat flow given off from small skin areas, the mean error of the method being only ± 0.0001 cal. cm.^{2} sec.$^{-1}$ The new "Strömungskalorimeter" constructed by Hensel (4) can be used clinically also for the determination of the blood flow through the skin. For details, see Hensel's monograph "Physiologie der Thermoreception" in *Ergebnisse der Physiologie* (5).

The depths of cold receptors in the tongue of the cat have been recorded in an objective way by Hensel, Ström, and Zotterman (6). This method is based on the recording of the spike potential of specific cold fibres in the lingual nerve set up by applying rapid cold jumps to the tongue and by simultaneous recording of the temperature changes. The depth of the cold receptors was calculated from determinations of (*a*) the threshold, (*b*) the temperature change of the thermode, (*c*) the latency of the specific cold spikes, (*d*) the thermal diffusion coefficient of the tongue. From a great number of measurements on the tongue of the cat, a mean value of 0.18 mm. ± 0.04 was obtained. The cold receptors are thus situated closely beneath the epithelium. At this depth an abundance of afferent nerve endings of various configurations have been described by histologists [cf. Sanders (7)]. The investigations of the receptive field for thermoceptors has often led to much debate. The question is, as Jenkins (8) formulates it, whether it should be compared with an unsensitive surface with spread circumscript sensitive spots or rather as a continuum with peaks, valleys, and plateaus. The peaks should then correspond to the spots according to the classical view. Hensel (5) maintains

[1] The survey of the literature pertaining to this review was concluded in June, 1952.

that a definite answer cannot be given as yet, because of the inadequacy of the employed methods of stimulation and particularly the use of small-sized thermodes, and further because of the complication brought about by the central threshold of conscious thermal sensations, which lies higher than the peripheral threshold of the single thermoceptors. Definite answers to this question can only be gained by applying new methods with exact control of the intracutaneous diffusion of heat simultaneously with recording of the impulse traffic in single temperature nerve fibres.

Bing & Skouby (9) have investigated the number of cold spots within an area of 6 cm.^{2} in man, using Blix's classical method at various skin temperatures. In one series of experiments, the number found increased from 17 to 93 spots with a rise in temperature of the skin from 25° to 33°C. This they believed to be due to both an increased excitability of spots from which a reaction can be elicited at lower temperatures and a reaction from spots in areas from which it is possible to induce reaction at high skin temperature only. A possible explanation might be that the rate of steady discharge, as well as the excitability of cold receptors, steadily increases from 27° to 32°C. Bing & Skouby do not give any data concerning temperatures above 30°C. However, it might be possible that the discharge of some cold receptors when using the Blix's cone will not become excited at the lower temperatures especially if the receptors should be more deeply situated. Further, some of them may be stimulated but to such a low degree that the discharge does not reach the level of the central threshold. When the temperature is raised from 20° to 32°C., a considerable increase in the discharge must occur.

In a second paper these authors (10) have examined the number of reacting cold spots in skin of the forearm in normal subjects before and after the application of acetyl-β-methylcholine, acetylcholine chloride, atropine sulphate, and prostigmine. Control experiments were perfomed on the same subjects using injections of 0.9 per cent NaCl. Acetyl-β-methylcholine (0.3 to 10 μg.) caused 5 to 20 min. later an increase in the number of reacting cold spots of up to 120 per cent of the initial value. Larger doses (100 μg.) produced an opposite result. The effect of acetylcholine was statistically not significant. Atropine sulphate injection (50 μg.) produced after 25 to 35 min. an average decrease in the number of reacting cold spots of 51 per cent of the initial value as compared with 7 per cent in the control experiments. Prostigmine injections ($0.5\times10^{-2}-0.5\times10^{-4}$ μg). produced 20 to 40 min. later maximum increases of 164 per cent.

These changes in the number of reacting cold spots were shown to have no connections with vasomotor reactions in the skin but were believed to be entirely due to a direct effect of the acetylcholine, either on the cold receptors or on the nerve fibres connected with them. They further maintain that the effects of atropine and prostigmine showed that changes in the concentration of the active acetylcholine found in the skin may influence the number of reacting cold spots. Injections of epinephrine reduced the number of cold spots 45 to 100 per cent. Ergotamine, hydergin (hydrogenated ergot

alkaloids), or dibenamine [*N*-(2-chloroethyl) dibenzylamine hydrochloride] were without any effect on the cold spots. Finally, the authors advance the hypothesis that the fall in number of cold spots observed as the skin temperature fell should be due to a lowering of the acetylcholine concentration of the skin. The latter might be brought about by vegetative impulses released by the influence of cold, which, by reflexes in the skin or via the central nervous system, reduce the number of stimuli liberating acetylcholine, including the vasodilating impulses by which the skin temperature of the area is simultaneously reduced. In this way the cold spots of the skin would be of importance for the local regulation of the loss of heat from the organism.

That the injection of acetylcholine, as well as acetyl-β-methylcholine, really affects the cold receptors has recently been confirmed by Dodt, Skouby & Zotterman (11) who recorded an obvious increase in the stationary discharge of cold impulses from single cold fibres of the cat's tongue. Thus, injections of very small amounts of acetylcholine, 1 μg. or less, produce a definite increase in the cold receptor discharge. Injections of larger doses of acetylcholine lead to an initial depression of the cold receptor discharge to steady temperature, as well as to temperature jumps, followed by a later increase of excitability and a rise in the upper threshold temperature. The action of acetylcholine seems to be very similar to that of menthol (see below). That acetylcholine in very minute doses injected in the common carotid artery stimulates the chemoceptors of the carotid body has been shown by Landgren, Liljestrand & Zotterman (12) which strengthens the view that acetylcholine might have something to do with the initiation of afferent impulses.

The Discharge of Cold Receptors at Constant Temperatures

The tongue of cat and dog offers special advantages for the studies of thermoceptors. The nerve is easily accessible and the tip of the tongue is very rich especially in cold receptors. Spike potentials of single cold fibres were first recorded by the reviewer (13). Judging from the relative spike height, the specific cold fibres are fibres 2 to 5 μ in diameter thus belonging to the δ-group. The specificity of these cold fibres has been confirmed by recent works of Hensel & Zotterman (6, 14). Splitting up the lingual nerve in fine strands often led to nerve preparations which permitted a quantitative study of the correlation between the single fibre discharge and the temperature of the receptor. In the first of this series of papers (14), in which the temperature of the thermode resting on the surface of the tongue was recorded thermoelectrically, it was shown that when the thermode was kept at a temperature below 23°C. the cold impulses never ceased although the temperature was kept constant for periods of more than 1 hr. Rewarming the tongue caused an immediate cessation of the impulses. Thus it was stated that the cold receptors within a certain range of temperatures discharge continuously when the receptors are kept at an absolute constant temperature. The effect of the circulation was eliminated by bilateral clamping of the lingual artery. The

findings were in agreement with the sense physiology results in man previously described by Hensel (3), and also with the experiences of everyday life, that below a certain temperature complete adaptation no longer occurs.

The results show further that a stimulation of the cold receptors is possible not only by energetic changes but also by a constant thermal energy stream after reaching a thermal steady state. In this state there is no temperature change but a temperature gradient between the different layers of the tongue.

The opinion that the intracutaneous temperature gradient is adequate stimulus for the thermoceptors seems to have originated from Ebbecke (15). It is essential however, to distinguish between the differential coefficient with respect to time $d\theta/dt$, i.e., the temporal gradient, and the spatial gradient $d\theta/dx$. Hensel & Zotterman (16) recorded the specific cold spikes from the lingual nerve of the cat when cold stimuli were applied to the tongue so as to cause negative or positive intracutaneous temperature gradients (spatial gradients). This can be done by cooling either the upper or the lower surface of the tongue in a way analogous to that employed by Bazett & McGlone (17) on the prepuce. Nerve preparations which contained cold nerve fibres supplying only the upper surface of the tip of the tongue were selected for the experiments. When the lower side of the tongue was cooled, no immediate impulses could be observed, but when the cold had penetrated the tongue and reached the upper surface after a lapse of 1.5 to 3.0 sec., cold impulses appeared with increasing frequency. When the lower surface was rewarmed, the cold impulses persisted at first until the upper surface was also warmed again. The arrest of the blood circulation in the tongue had no primary influence on these findings. Cooling by means of injecting cold Ringer solution into the lingual artery produced the same cold receptor discharges as cooling from the surface. These experiments clearly showed that the stimulation of the cold receptors does not depend upon the direction or slope of any intracutaneous temperature gradient but simply on the cooling of the receptor layer.

A more quantitative study of the relation between the single cold fibre discharge and the temperature of the receptor was made in another paper by Hensel & Zotterman (18). The behaviour of single cold receptors at constant temperatures from 17° to 40°C. was studied in detail (see Fig. 1). The stationary discharge showed a maximum frequency of about 10 impulses per second. The site of this maximum on the temperature scale varied. The upper temperature at which the cold receptors displayed a steady response at constant intracutaneous temperature was called the "stationary threshold temperature." This threshold varied. Thus single receptors still discharged continuously, although at a very low rate, at 41°C. which is above ordinary blood temperature. The threshold and maxima of the steady discharge show various thermal distributions for the single fibres.

Generally the maximum discharge was found at 30 to 32°C. Between the maximum and the upper threshold is usually a lapse of only 7°C. From the

general shape of the stationary discharge curve of a typical cold receptor, it can be understood that the steady discharge of cold fibres must increase when the temperature is raised from low temperatures towards temperatures of about 30°C. This will partly account for the persisting sensation of cold experienced when a cold object has been pressed for a while against the forehead, for example, and removed—Weber's phenomenon of the persisting cold sensation [Hensel & Zotterman (19)].

Dodt (20), in the reviewer's laboratory, has particularly studied the activity of single cold and warm fibres at physiologically extreme temperatures. In these experiments he discovered that the single cold fibre discharge did not decrease continuously below 15°C. but shows a secondary peak of about two-thirds of the maximum frequency in the range of 15° to 10°C. (see Fig. 1). This latter sensitivity increase covers 2° to 3° of the centigrade scale. Continuous activity of the cold receptors below 8°C. was absent in all cases. The cold paralysis [cf. Gernandt & Zotterman (21)] appeared in the majority of cases when the temperature of the thermode lay between 10° and 12°C.

Thauer & Ebaugh (22) have recently determined the thresholds of discrimination of temperature sensations in man by means of the radiometer invented by Hardy (23). At skin temperatures of 31° to 33°C., the thresholds were constant for the cold receptors, whereas they increased considerably when the temperature rose from 33° to 35.5°C. This is quite incompatible with the classical theory of Weber but in close agreement with the electrophysiological studies of Hensel & Zotterman (14, 16, 18, 19) on the correlation between the excitability and the temperature of cold receptors.

The Response of Cold Receptors to Temperature Changes

Rapid cooling raised the frequency of discharge of a single cold fibre to about 140 impulses/sec. [Hensel & Zotterman (18)], a value which is about ten times as high as the maximum frequency of the steady discharge at constant temperature. The effective stimulus for this overshooting excitation is thus the rate of change, $d\theta/dt$, contrary to the final frequency attained at constant temperatures which is determined entirely by the absolute temperature. When cooling suddenly, it was even possible to obtain a cold fibre discharge at temperatures above the upper threshold temperature of the cold receptor. In such cases the cold fibre discharge soon disappeared, i.e., adapted to zero. Applying cold jumps of 2°C. at various initial temperatures, it was found that identical intracutaneous temperature changes elicited different grades of excitation in the cold receptors depending upon the range of temperature within which the change occurred. Between the initial and final frequency within certain ranges of temperature an approximately linear relation was observed. Thus for cold jumps of 1°C., the relation between initial and final frequency was 3:1, and for cold jumps of 2°C., abut 6:1.

Rapid warming of the cold receptors to a constant temperature led to an immediate cessation of the steady discharge. If the final temperature lay below the upper threshold temperature for the steady discharge, the impulses

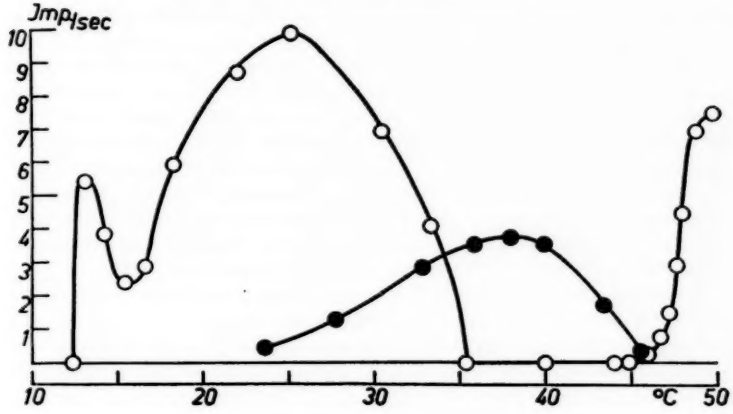
reappeared and adjusted themselves at a frequency corresponding to the prevailing temperature. The length of this pause caused by warming the cold receptors depended upon the rate of warming and the range of temperature. If the warming was very small or followed at a relatively slow rate, the cold impulses might not disappear at all but occur only at a lower frequency during the warming. Thus cold impulses may appear even during warming the cold receptors. This is what happens according to Hensel & Zotterman (19) when the persisting cold sensation is experienced after removing a cold object from the skin.

The principal features of the response of cold fibres to constant temperatures as well as to rapid changes of temperature of the receptors are depicted in the diagram of Figure 2, which shows the impulse frequency of a single cold fibre as a function of time when the temperature of the receptor is changed stepwise between the three constant temperature levels of *a*, *b*, and *c*. All these levels are chosen below the upper stationary threshold temperature. At the constant temperature, *a*, the receptor discharges at a constant rate of a^1. At the moment t_1 the temperature of the tongue is suddenly cooled to the constant level of *b*. This produces an immediate rise of the frequency which then attains a new final value of b^1 at a higher frequency than a^1. At the moment t_2, the temperature suddenly returns to the original level of *a*, which makes the impulses disappear immediately, whereafter they slowly reappear to attain finally the original frequency of a^1. When the temperature falls to a deeper level *c* (broken line) the overshooting discharge as well as the final discharge c^1 will be greater. At the return to the temperature *a*, the duration of the impulse free interval, "the postexcitatory depression," as well as the time for attaining the final frequency value of a^1 will increase considerably. The temporal course of the curve in t_1 is rather accurately the mirror image of that in t_2, but for the fact that for obvious reasons the curve at t_2 cannot become negative but is cut off at zero. We presume, however, the appearance at t_2 of some inhibitory processes symmetrical with the excitatory processes at t_1. This postexcitatory depression depends upon the strength and duration of the previous excitatory process which has been further elucidated by Dodt (20) in this laboratory.

This behaviour of the cold receptors is in general agreement with that of the baroceptors of the carotid sinus as described by Landgren (24). The curve of Figure 2 also shows a general similarity to the configuration of the receptor potentials of the muscle spindle as recorded by Katz (25, 26).

Warm Receptors

The original finding (13) that warm sensations are mediated by fibres at somewhat greater diameters than those of cold has been confirmed by Hensel & Zotterman (27). The warm fibres of the cat's tongue have been subjected to a closer electrophysiological investigation by Dodt & Zotterman (28). It was found that single warm fibre preparations were best prepared by



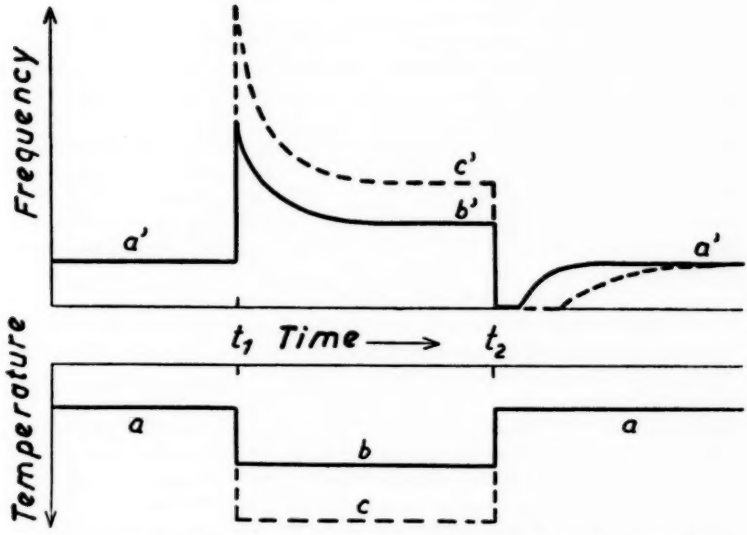


FIG. 1. (Above) Graph showing the frequency of the steady discharge of a single cold fibre (open circles) and of a single warm fibre (filled circles) when the receptors were exposed to constant temperatures within the range of 10 to 50°C.

FIG. 2. (Below) Graph showing the discharge of a single cold fibre as a function of time at different changes of temperature. For further explanation see text.

splitting up the tympanic chorda or the posterior branches of the lingual nerve.

The warm receptors were usually found to give a steady discharge when exposed to constant temperatures from 20° to 47°C. The lower temperature represented regularly the lower threshold temperature while the upper threshold temperature varied in different units. Below 20°C. and above 47°C., no steady discharge was noticed. The maximum rate of discharge was found to lie between 37.5° and 40°C. (see Fig. 1). The steady discharge was rather irregular, which may suggest that several receptors are connected to the same afferent nerve fibre [Weddell (29)]. The maximum frequency varied in single warm fibre units between 1.5 and 3.7 impulses per second.

A sudden rise in temperature produced an increased frequency of impulses, the extent of which was dependent upon the rate of change and the height of the rise in temperature. Such an initial outburst of impulses was seen even when the temperature was suddenly raised to values above the upper threshold for the stationary discharge. When the tongue was repeatedly exposed to sudden heating above 40°C., the initial discharge at the warm fibre became progressively smaller because of the depressing action of the high temperature. A similar phenomenon concerning the reversible action of heat on the touch receptors was observed by Zotterman (13).

When the temperature suddenly falls more than 8° to 15° of the centigrade scale, some warm fibres, probably the most superficially situated, give off a sudden discharge of phasic character. This discharge has a relatively short latency and reasons were given to show that this effect is due to an inadequate stimulation of the warm receptor or perhaps more likely of the most peripheral part of its nerve fibre. The different single warm fibre preparations displayed a variety of latencies to the same rise in temperature which was believed to be due to variations of the depth of the warm receptors in the tongue.

Paradoxical Sensations

While it is agreed that stimulation of cold spots by heat above 45°C. leads to a sensation of cold, it is still debated whether a corresponding paradoxical heat sensation results from stimulation of warm spots by cooling. Dodt & Zotterman (30) studied the discharge of single cold fibres when temperature of the cat's tongue was raised to 45°C. and more, and found a steady discharge to constant temperatures (see Fig. 1). The threshold value of this paradoxical discharge of the cold fibers lies at about 45°C. and a maximum frequency of 7 to 7.5 impulses per second is attained at 50°C. The lower threshold temperature of this paradoxical cold discharge lies always about 45°C., that is, a good bit above the upper limit of the usual range of temperatures within which the cold receptors display a steady discharge. Paradoxical excitation of cold receptor at temperatures below 45°C. does not occur. The cold sensation which appears after a rise in the skin temperature from 20° to 35°C., as described by Thunberg (31), is not due to any paradoxical excitation but to a reappearance of the usual steady discharge of cold impulses

when the temperature approaches the final value of 35°C. This phenomenon is another example of the "persisting cold sensation" analysed recently by Hensel & Zotterman (19).

A paradoxical response of specific warm fibres to rapid cooling of 8° to 15° of the centigrade scale, has been recorded by Dodt & Zotterman (28). This discharge has, however, more the character of an off-discharge of phasic nature. The more rapid the change in temperature, the more conspicuous it was, but it appeared even at rather slow rate of cooling. The response soon fades away when the temperature is kept below 20°C. A steady discharge of warm fibres could not be produced at temperatures below 20°C. Another characteristic feature of this paradoxical discharge of warm fibres is its very short latency when the temperature drops quickly.

The phasic discharge and the short latency suggest that the paradoxical warmth might be an affair of the nerve fibres and not of the warm receptors themselves. Bernhard & Granit (32) originally discovered that rapid cooling of a nerve stem excites class A fibres directly and this discharge displays exactly the same features as the paradoxical warmth.

Goldscheider & Hahn (33) suggested that cold objects are felt to be heavier than warm ones (Weber's illusion) because of a concomitant stimulation of mechanoceptive fibres by the cooling. Experimental evidence for this suggested explanation was obtained by Hensel & Zotterman (34).. They found that fibres giving fairly large spikes (8 to 10 μ) respond to rapid cooling of the tongue in nerve preparations which responded to pressure. However, the largest afferent fibres (12 to 15 μ) did not respond to cooling at all. The mechanoceptive fibres do not respond except to very low temperatures and rapid cooling, whereas the cold fibres are able to respond to cooling of some tenths of a degree below 40°C. The most important difference is, however, that whereas the response of the mechanoceptors to cooling disappears very quickly, the cold receptors keep on responding with constant frequency as long as a constant low temperature is maintained. The most likely explanation is that this inadequate stimulation of the most superficially located mechanoceptive fibres is not an affair of the receptor itself but, in analogy with the paradoxical warmth, is due to a direct action upon the most peripheral part of the nerve fibre itself.

Katz (35) describes an experiment on thermal receptors of the penis in man which greatly strengthens the original view of Alrutz (36) that the sensation of "heat" is due to a combined stimulation of warm receptors and a paradoxical stimulation of cold receptors. The fact, however, that the warm receptors very soon cease to discharge at temperatures above 43°C. have induced Dodt and the reviewer (28) to believe that the sensation "hot" is initiated by warm and paradoxical cold impulses but maintained by cold and pain impulses. This is in accordance with the old observation of Hacker (37) who found that in a skin which was deprived of all cold spots and contained warm spots only, temperatures above 45°C. did not produce any sensation of heat.

The Ebbecke Temperature Phenomena

The duration of the post excitatory depression of the cold impulses after equal rises in the thermode temperature between 10° and 40°C., Dodt (20) found to be maximal between 23° and 25°C. and again between 15° and 17°C., but to be nearly or completely absent between 10 and 15°C. Therefore, on raising the temperature through the high sensitivity zone between 10° and 15°C., cold impulses, even with rapidly increased skin temperature, are recorded which cease temporarily when the temperature reaches 15°C. or more.

The behaviour of the cold fibre explains the phenomenon which Ebbecke (38) described in 1917; when an ischaemic limb is greatly cooled down for several minutes and the blood supply then restored, a sensation of cold was regularly experienced.

The other phenomenon described by Ebbecke—that the restoration of the circulation to a heated limb gives rise to a sensation of warmth, although the temperature of the limb is lowered by the blood flow—can, according to Dodt (20), be explained in various ways: (*a*) If the temperature lies at the upper limit at which continuous warm fibre discharge is found (e.g., at 45°C.) then on cooling the skin moderately an immediate "return of warm discharge after the onset of heat paralysis" is observed. (*b*) If the initial temperature is higher (48 to 51°C.) then, on moderate cooling, a "return of the warm discharge after heat paralysis" occurs, but only after an interval of several minutes [cf. Zotterman (13)]. (*c*) If the initial temperature is lower (e.g., 37 to 40°C.), then the warm fibre activity returns a few seconds after moderate cooling ("postexcitatory depression of the warm fibre activity"). (*d*) A discharge of phasic type ("paradoxical warm discharge") appears immediately after more considerable cooling. Its intensity is approximately proportional to the difference between the initial and final temperatures. Maintaining a high initial temperature (45 to 50°C.) for a longer time before the rapid and considerable cooling is begun, increases the duration of these phasic discharges up to 5 sec. These last findings show that the temperature sensations studied by Ebbecke were the result of returning discharges partly modified by extreme temperature of the limb at the moment its circulation was restored. Some of the various characteristics of the behaviour of warm and cold spots are summarized in Table I.

The Action of Menthol

The well-known sensitizing effect of menthol upon cold receptors was studied by Hensel & Zotterman (27) who investigated the impulse traffic of cold fibres after the application of menthol on the tongue of cat. Aqueous menthol solutions of 1:10,000 led to strong stationary discharge of the tongue's cold receptors at constant, warm temperatures, at which, without menthol, there was no discharge. At lower temperatures at which the cold receptors are stationary, discharging without menthol, this substance produced a great increase of the cold impulse frequency. The effect of menthol

TABLE I

COMPARISON OF THE CHARACTERISTICS IN THE BEHAVIOUR OF WARM AND COLD FIBRES*

Warm receptor	*Cold receptor*
(*a*) Steady discharge at constant temperatures between 20° and 47° (50°) C. Maximum frequency of this generally tween 38° and 43°C.	(*a*) Steady discharge at constant temperatures from about 10° to 41°C. Maximum frequency of this usually between 25° and 35°C.
(*b*) Maximum frequency of the steady discharge from a single fibre in response to a constant temperature 3.7 per sec.	(*b*) Maximum frequency of the steady discharge from a single fibre in response to a constant temperature 9.8 per sec.
(*c*) Aperiodic discharge of impulses in response to a constant temperature.	(*c*) Periodic discharge of impulses in response to constant temperatures.
(*d*) Sudden heating of the skin produces a rapid volley of impulses	(*d*) Sudden cooling of the skin produces a rapid volley of impulses.
(*e*) "Paradoxical" discharge of phasic character in response to a fall in temperature of more than 8° to 15°C.	(*e*) "Paradoxical" steady discharge in response to constant temperatures of 45° to 50°C.

* From Dodt & Zotterman (28).

can be completely compensated for by sudden heating or by keeping the tongue at a constant higher temperature as these measures can cause the cold impulses elicited by menthol to disappear entirely. Thus, it is not simply the question of a chemical "inadequate" stimulation of the cold receptors (the warm receptors are not affected) but of a sensitization of the thermal effect. The threshold of the menthol effect lies between a concentration 1:1,000,000 and 1:500,000. It is thus likely that the action of menthol concerns some enzymatic process in the cold receptors.

THEORIES OF THERMOSENSATION

The elaborate measuring of the diffusion of heat in the skin made by Hensel (2, 3, 39, 40) as well as the recent experiments by Marechaux & Schäfer (41) have shown that Weber's classical theory can no longer be upheld.

The electrophysiological findings do not satisfy the different spatial gradient theories of Ebbecke, Bazett, and Rein, nor the classical temporal gradient theory of Weber. Particularly the discovery of a steady discharge at constant temperature does not coincide with Weber's theory. It has also been widely recognised that it would seem very impractical if the cold fibres really reacted according to this theory as it would be very difficult to operate the thermostat of the body if the cold receptors adapted fully at usual skin temperatures.

The behaviour of the mammalian thermal receptors is in many respects very similar to that of Lorenzini's ampullas of Raja which were discovered by Sand (42) to be of thermoceptive function.

The factors governing the inflow of thermal impulses are, according to Hensel & Zotterman (18), the rate of the temperature change, $d\theta/dt$, the temperature, θ, and the area F, which can be expressed as following

$$E \ni f(\theta, d\theta/dt, F)$$

where E is the abstraction class of the sensation threshold, $\ni$ the implication sign of a probability implication [Renqvist-Reenpää (43) and Reenpää (44)]. A sensation of cold would thus occur when (*a*) θ is low, (*b*) the rate of cooling, $d\theta/dt$, is sufficient, and (*c*) the receptive field, F has a certain area. The recording of the action potentials from peripheral cold fibres shows that the total number (n) of impulses which in the time t arrive at the central organ also is a function of these three factors,

$$\frac{n}{t} \ni \phi(\theta, d\theta/dt, F)$$

i.e., the value of n/t becomes greater when (*a*) the temperature is colder, (*b*) the rate of cooling is greater, and (*c*) when the receptive field is enlarged—i.e., when the number of stimulated cold receptors is increased. The rate of n/t is nothing else but the central threshold which thus can be written,

$$E \ni \psi\left(\frac{n}{t}\right).$$

At constant temperature of the skin, the magnitude of n/t is dependent upon the absolute temperature and the area of the skin. If the thermal receptors were evenly distributed, the thermosensible tonus would thus be a direct function of the integral skin temperature. This is, however, not the case as some parts, especially the trigeminal area, display a much greater density of thermal receptors and are thus likely to exert a more dominant influence upon the thermoregulation of the body. It is very likely that the central threshold of the conscious cold sensations lies higher than the threshold of the cold fibre discharge [Hensel & Zotterman (18), Grant (45)] which implies that a certain part of the afferent thermoregulatory inflow occurs below the threshold of our consciousness.

The impulse frequency of the cold receptors does not follow van't Hoff-Arrhenius law but rises with increasing temperature to a certain level and then falls off again as will be seen from Figure 1. Hensel & Zotterman (18) have taken the course of the cold receptor discharge and particularly the response to temperature changes, as a pretext for developing a hypothesis that the receptor discharge is governed by at least two different processes,

one excitatory and one inhibitory. The overshooting excitation which occurs when the temperature is rapidly decreased as well as the postexcitatory depression following changes in opposite direction can only be explained by assuming the interacting of two such antagonistic processes. A similar scheme was already suggested by Sand regarding the activity of Lorenzini's ampullas of Raja (42). For further development of this theory, see the monograph of Hensel (5).

Central Thermosensitive Structures

In recent years our knowledge of the thermosensitive apparatus in the hypothalamus has been greatly increased and can be studied in the excellent surveys by Thauer (46), Blair & Keller (47), Mansfeld (48), Keller (49), Folkow, Ström & Uvnäs (50, 51), Eliasson & Ström (52), Ström (53 to 57) O'Connor (58, 59), O'Connor & McKeever (60), Hardy (1), Grant (45), Robinson (61). All agree that very small increases in the temperature of the hypothalamic centres lead to vasodilation in the skin while, on the other hand, even a very substantial cooling of the heat centres does not elicit any more definite reactions. Euler (62) has succeeded in recording slow potential changes from the hypothalamus in response to warming. The thermosensitivity of these ganglion cells is remarkably high. Temperature rises of 0.1°C. produce potential changes of 0.5 to 1 mv. He further demonstrated that there is a close correlation between the height of the potential and the degree of panting of the dog. It is therefore tempting to suggest at present that the general feeling of warmth might be principally elicited normally by the centrogenic action of the blood temperature. Another feeling of "general origin," thirst, is no doubt produced centrogenically according to the experiments by Andersson (63, 64) who found that the injection of 0.1 ml. of a 1.5 per cent NaCl solution directly into the anterior medial region of the hypothalamus in the unanesthetized goat produced an almost immediate uptake of several liters of water. The effect could be repeated on renewed injections. Hypotonic or isotonic solutions failed to produce polydipsia. The same applied to hypertonic solutions in the posterior and lateral parts of the hypothalamus. Thus the existence in the anterior hypothalamic region of specific cells sensitive to osmotic changes must be assumed, cells which control the uptake of water by producing a sensation of thirst.

The relatively small number of warm receptors and the relatively low rate of their stationary discharge compared with that of the cold receptors [Dodt and Zotterman (28)], would rather suggest that the afferent warm fibre tonus acting on the thermoregulatory centres should have much less effect than that of the cold fibre system. Thus the body thermostat should be governed principally by the centrogenic heat effect and by the cold impulse inflow and, but to a minor degree, by the warm fibre influx which previously has been suggested by Grant (45). Hensel (5) also believes that the tonus of the "heat centres," which determines the intensity of the thermoregulation, should be a function of the inflow of afferent impulses as well as of increased

excitability of the centres influenced by the blood temperature, an idea originally expressed by Rein (65). Hensel (5) further draws attention to the fact that regulation of the body temperature differs in a characteristic way from technical thermostats in that the intensity of heating or cooling is graduated. Further, and still more important, the sensitive organs of the regulator are not only regulated in a central place but also in the periphery where the cooling begins. In that way the regulation against external temperature changes will start before these have reached the body inside. In this respect the very sensitive trigeminal area, immediately exposed to all weathers, has its special importance as the receptive field. Hensel (66) has just shown that the cold receptors of the trigeminal area of cat display in every respect the same functional characteristics as those of the tongue. Therefore, the general scheme of the function of thermal receptors as developed from the investigations on the lingual temperature nerve fibres can be applied to the thermal fibres of the skin.

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PHYSIOLOGY OF VISION[1,2]

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It is not intended in the present review to cover all the literature on vision during the past three years. Selection of materials has been made with the view of bringing out more effectively the main trends in vision study and the pre-eminent advances achieved in some particular fields of interest. Omitted are the papers, such as those on ocular movements, pupillary reflexes, chemical and metabolic changes of the eye in general, electroencephalography of the visual cortex, psychological tests of visual functions, etc., which either are not directly related to the physiology of vision or are more relevant to other chapters of this volume. Some other important works may have been left out. This exclusion reflects nothing more than the reviewer's lack of access to those papers.

During the period for which this review is made there appeared a number of review articles and monographs dealing with various aspects of vision, among which notably are Hartridge's *Recent Advances in the Physiology of Vision* (71, 72) and Granit's reviews on retinal organization (62) and physiology of vision (63). Some review articles on the psychological aspect of vision appeared successively in the first three volumes of the newly founded *Annual Review of Psychology* [Bartlett (9); Chapanis (33); Helson (75)]. Articles on some specific topics of vision appeared regularly in *Documenta Ophthalmologica* and occasionally in *Ophthalmic Literature.*

PHOTOCHEMISTRY OF RETINA

The present status of our knowledge of the rhodopsin system was critically reviewed by Wald (173) in whose laboratory many of the recent advances in the chemistry of rod vision have been made. One of the significant findings is probably the recognition of the subsidiary roles played by an enzyme system in the synthesis of rhodopsin from vitamin and retinene [Wald & Brown (175), Bliss (19)]. It is shown that in the outer segment of the rods retinene, the product of rhodopsin by the action of light, is reduced to vitamin A by an enzyme system in which retinene reductase plays an important role and cozymase (diphosphopyridine nucleotide) acts as a coenzyme (19). It is also shown that in the process of rhodopsin regeneration vita-

[1] These studies were aided by a contract between the office of Naval Research, Department of Navy and Yale University (NR 112-002).

[2] The abbreviations ERG (electroretinogram) and ICI (International Committee on Illumination) are used in this chapter.

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min A is oxidized to retinene by the action of the oxidative system and cozymase [Walt & Hubbard (179)]. The addition to retinal homogenates of the succinoxidase system of heart muscle, for instance, promotes greatly the oxidation of vitamin A to retinene, and thus increases the yield of rhodopsin by about 33 per cent or even 55 per cent if the pigment layer homogenate is also added. Pigment layers of the eye seem to contain also an enzymic factor; but the beneficial effect of the epithelium on rhodopsin synthesis is believed to be due mainly to its supply of vitamin A to the retinal tissue [Hubbard (80), Hubbard & Wald (81)]. The fact that breakdown and formation of rhodopsin in the living eye depends upon oxidative and reductive processes with the aid of enzyme and coenzyme systems indicates the importance of retinal respiration in the maintenance of normal vision. The energy required for carrying out the transformation of rhodopsin and its precursors is supplied by both aerobic and anaerobic glycolysis [Tansley (160)]. By using the action potential of the visual apparatus as an index of retinal function, it was found that the ERG[2] failed to appear in about 20 min. when the oxygen supply was removed [Noell & Chinn (132, 134)] and the retina ceased to function within 2 to 4 min. after a single dose of 15 to 25 mg. per kg. of intravenous sodium iodoacetate which is known to impair preferentially the metabolic process taking place in the absence of oxygen [Noell (133)]. Azide, another enzyme inhibitor, showed a similar effect on the visual function [Noell (131)]. The light-adapted retinae were found to contain more creatine and less phosphocreatine than the dark-adapted ones, a fact suggesting an energy producing mechanism of phosphocreatine breakdown and synthesis during the cycle of visual purple transformation [Hwang 87)].

Several substances present in the intermediate stages of the transformation between rhodopsin and vitamin A have received considerable attention. Retinene, the substance extracted from the freshly bleached retina, is apparently preceded by an unstable substance "transient orange" which, on warming, changes to "indicator yellow." The relationship of retinene and its precursors has been elucidated in a series of papers by Collins & Morton (40, 41, 42). These authors showed that retinene would combine with various amines to form compounds closely resembling indicator yellow which on hydrolysis would form retinene. The absorption maximum of alkaline indicator yellow is 365 mμ and that of the acid indicator yellow is 440 mμ. The absorption spectra of indicator yellow in the near-ultraviolet region have been largely confirmed by Peng & Chian (141); these men found that the λ_{max} of indicator yellow are 440, 400, 380, 370, and 370 mμ at respectively pH 5.2, 6.1, 7.1, 8.2, and 9.0–10. From the changes of spectral absorptions of the acid and alkaline reactions of rhodopsin and its allied substances the chemical structures for indicator yellow and rhodopsin chromophoric group were proposed by Collins & Morton (41, 42). Those structural formulae show that the conversion of rhodopsin to indicator yellow is an oxidative process involving the loss of two electrons. From this hypothesis it is assumed that

the absorption spectrum of isorhodopsin is due to a single rhodopsin chromophoric group on the protein, while that of rhodopsin is due to two chromophoric groups adjacently situated on the same protein molecule and interacting to some extent.

A possibility has been suggested by Berger & Ségal (15) that the processes involving the two intermediate substances may go on in parallel, instead of in succession, in the synthesis of the visual purple, according to the conditions of bleaching. From the characteristics of scotopic luminosity curves taken (*a*) after a brief exposure to an intense light, and (*b*) after prolonged exposure to a moderate light, they inferred that visual purple regeneration is mainly from transient orange after a short intense bleaching and from indicator yellow after a prolonged illumination.

Recent studies by Hubbard & Wald (82) indicating that only the *cis*-form of retinene or of vitamin A is capable of resynthesizing rhodopsin have introduced an entirely new factor in the biochemistry of vision. It has long been known that the usual preparations of crystalline vitamin A, which are mainly stable *trans*-form isomers, are ineffective in the synthesis of rhodopsin, whereas the vitamin A prepared from the fish liver oil which contains some *cis*-isomers is comparatively effective. When a solution of vitamin A is isomerized by light in the presence of a trace of iodine it becomes as efficient a precursor of rhodopsin as the liver oil extract. The newly found retinene in the bleaching of rhodopsin is probably *trans*-form in configuration and is ineffective in rhodopsin synthesis in the dark. The stereoisomerization of retinene can be achieved by the action of the light with shorter wave length but not by that of the light of longer wave length. This, however, seems to be at variance with the fact that vision continues very well in yellow, orange, and red light in which no isomerization takes place. In explaining the mechanism of rhodopsin turnover *in vivo*, Hubbard & Wald suggested that the eye must be continually supplied with active isomers of vitamin A from the blood circulation, which in turn takes it from stores in the liver and, ultimately, from the nutrition. In the process of seeing, the retina continually uses up the active isomers of vitamin A from the circulation and returns to the blood the inactive, di-*trans* isomer.

A further step forward in the understanding of the chemical mechanisms of visual purple synthesis has been made by the discovery of the role played by sulfhydryl groups. Previously, Morton found that retinene is vitamin A aldehyde which readily reacts with the —SH groups of cysteine and glutathione in the protein complex. Probably with this clue in mind, Wald & Brown (178) found that the bleaching of rhodopsin by light exposes two —SH groups on opsin for each retinene$_1$ molecule liberated. These sulfhydryl groups, according to Wald & Brown, are concerned directly in binding the chromophore to opsin and furnish hydrogen atoms for the reductive change in the synthesis of rhodopsin from retinene$_1$ and opsin. Evidence supporting this hypothesis is the fact that the condensation of retinene$_1$ with opsin to form rhodopsin is optimal at pH about six, an

acidity which favors condensation of retinene$_1$ with —SH rather than with amino groups. These authors further found that in the amperometric silver titration the bleaching of rhodopsin yielded direct electrical variations. This phenomenon may have some fundamental connection with the initiation of visual action potentials [Wald & Brown (176)].

The bleaching of rhodopsin, like all the other chemical processes, needs thermal energy to bring about the changes in molecular rearrangements. St. George (58) demonstrated that the bleaching rate of rhodopsin becomes temperature-dependent in red light. Apparently at long wave length the quanta are not sufficiently energy-rich to bring about bleaching by themselves. The absorption spectrum of rhodopsin, which is not markedly temperature-dependent at shorter wave lengths, also becomes temperature-dependent in red light of wave length longer than 570 to 590 mμ. This result may provide a partial explanation as to why the wearing of red goggles can help in subsequent dark adaptation [Mitchell (112)].

The visual pigments are different in different species of animals and even different in different parts of the retina of the same animal. Denten & Pirenne (50), for instance, described in the retina of *Xenopus* red and green colored rods. The green ones, constituting about one-thirtieth of the total number of the rods, are bleachable in white light, and can affect the spectral sensitivity curve and absorption curve of retinal extracts. In the dark-adapted tench retina there was found a new photosensitive visual pigment which absorbs maximally at the wave length 467 mμ and may be bleached with light of longer wave length. In coping with the increasing number of visual pigments [Krause (95)] and the inadequacy of existing nomenclature, Dartnall (45, 46) proposed a new nomenclature system based on the wave length of maximal absorption. For instance, iodopsin should be called visual pigment 565; visual violet (porphyrhodopsin), visual pigment 533; visual purple (rhodopsin), visual pigment 502; and the red sensitive pigment of tench, visual pigment 467. This system of nomenclature, though having certain advantages, should not be adopted unless and until the $\lambda_{max.}$ values for individual visual pigments are determined with purest preparations of which only a few are available.

ELECTROPHYSIOLOGY OF VISION

Entopic Response to Electrical Stimulation of the Eye

It has long been known that a subjective sensation of light, phosphene, can be aroused by electric current passing through the head. The threshold strength of the stimulating current for the production of phosphene has been found to vary with time after exposure of the eye to previous photic stimulation. By using this phosphene response as an index, the excitability of the human retina can be measured fairly accurately. The excitability curves, constructed by plotting the reciprocal of the threshold voltage of the stimulating current as ordinates and the time interval between the end of

preillumination and the onset of stimulation as abscissae, show that the maximum of excitability is reached at different intervals following preillumination according to the color of the light used, irrespective of the light intensity. For instance, in subjects with normal vision the values of the crest time are 1 sec. for red (650 mμ), 1.25 sec. for yellow (585 mμ), 2.25 sec. for green (530 mμ), and 2.75 sec. for blue (470 mμ). In color-blind subjects a certain crest may be absent or less prominent [Ebe, Isobe & Motokawa (54); Motokawa & Suzuki (124)]. This technique, therefore, avails itself as a very useful means of studying the problem of color vision. Motokawa and his associates have fully and successfully exploited this method and have thereby collected a vast amount of data concerning various phases of vision.

That the excitability of the retina changes after cessation of preillumination with a time course characteristic of the wave length of the light used has also been demonstrated in animals by means of a technique similar to that used for the human eye. However, in the former case the threshold for the action potential of the optic nerve, instead of that of subjective phosphene, is used as an index of excitation. The excitability curves thus determined in cats, resembling those obtained in humans, show maxima at 1, 1.5, 2.25, and 3 sec. when the preilluminating lights are respectively red, yellow, green, and blue [Motokawa, Iwama & Ebe (127)]. The red, green and blue elevations of the excitability-time curve are respectively at about 1.5, 3.0, and 5.0 min. in the frog [Motokawa & Iwama (123)] and at about 2.5, 6.5, and 11.5 min. in the toad [Tukahara (171)]. The color process in the retina of amphibians are markedly more prolonged than in the retina of mammals, presumably due to the low body temperature. It was reported in the cat that the excitability-time curve was greatly prolonged when the body temperature fell below certain levels [Motokawa, Iwama & Ebe (127)].

The latent period of perception time for the appearance of phosphene varies with stimulus intensity and the area of the retina stimulated. According to Hironaka (78) the latent period for the peripheral retina was considerably longer than that for the central retina, which led him to ascribe the cones as the site of stimulation. This result appears to be contradictory to Meyer-Schwickerath's findings (109) that the peripheral parts of the retina have a lower threshold for the flickering phosphenes aroused by faradic currents. Whether the discrepancy is due to the difference in parameters of stimulation is not known. Threshold values for subjective light sensation have been determined by Bouman, Ten Doesschate & van der Velden (25) by means of periodic rectangular electrical stimulation with variable frequency, duration, and intensity. They found that at a frequency 20 c.p.s. the threshold current intensity was at a minimum for short durations.

According to a study by Motokawa & Iwama (122) the threshold strength for a sensation of flickering phosphene caused by an alternating current passing through the head varies with the frequency of alternating current in a characteristic manner in which three minima of threshold

strength are located at 18, 37, and 53 c.p.s. With a similar method Abe (1) obtained a strength-frequency curve with five minima at 7, 20, 36, 55, and 75 c.p.s. in the light-adapted eye and with three minima at 7, 35, and 65 c.p.s. in the dark-adapted eye. In a most recent study there were revealed seven minima located at frequencies 20, 27.5, 35, 42.5, 52.5, 62.5, and 77.5 with the optimum frequency at about 20 c.p.s. By comparing the effect of retinal induction caused by colored lights and by alternating currents it was said to be possible to determine the functional correspondence between the frequency of alternating current and the wave length of the colored lights. Thus, blue, green, yellow, and red correspond respectively to the frequencies of 35, 42.5, 52.5, and 60 to 100 c.p.s. [Motokawa & Ebe (121)]. In view of the fact that a single electric shock applied to the eye is always followed by periodic changes in retinal excitability [Motokawa (119)], the variation of the strength-frequency curves described by Motokawa & Ebe might have been the result of a modulation of a series of the periodic excitability changes caused successively by individual pulses of the stimulating current. If that is the case, the significance of the minima in the strength-frequency curve would have to be reconsidered. The periodic oscillation of retinal excitability at a frequency of 18 c.p.s. as observed by Motokawa resembles closely the general phenomenon of periodic excitability changes in the central nervous system [Chang (34)]. This rhythmic excitability change may provide an explanation of the rhythmic blinking of small objects of constant light source in the distance [Remberg (146)].

The question of which element in the retina gives rise to the phosphene when the whole eye is stimulated through the head remains unanswered. The site of excitation is ascribed to the nervous synapses of the visual apparatus by Bouman, Ten Doesschate & van der Velden (25), to the cones alone by Hironaka (78), and to both rods and cones by Meyer-Schwickerath & Magun (110).

Electrical Responses of the Visual System

"On" and "off" effect.—Recent advances in the field of electrophysiology of the visual system have been technically marked by the wide application of microstimulating and microrecording techniques, and conceptually influenced by Hartline's and Granit's findings that retinal elements can be divided, according to their response to stimulation, into three types, namely: "on," "off," and "on-off" elements. The three types of fibers have been again identified in the optic nerve of rabbit [Thomson (167)]. Carrying on the traditions of Granit's laboratory, Bohm & Gernandt (22) made a comparison of the threshold values for the "on" and "off" responses from large ganglion cells, the neural network in the retina, and the lateral geniculate body. They found that the retinal network showed higher activity at "off" than the ganglion cells and the geniculate body. This apparently higher activity was thought to be due to the convergence of rod-dominated responses which are transmitted unchanged to the lateral geniculate body.

The "on" discharge is visual purple dependent and concerned with rods [Granit (62)], whereas the "off" discharge is thought to be concerned with cones [Tomita & Funaishi (163)]. In the opinion of Granit (60), the "off" discharge may arise as a result of release from the inhibition by another element, implying that the specificity of the retinal elements is not very rigid. In an analysis of the response from single retinal elements in the cat, Donner & Willmer (53) were impressed by the extreme complexity and variability with which the retinal elements respond to stimulation.

Most recent studies by Kuffler (96) demonstrate that the discharge pattern of the neutral elements is by no means fixed. "On," "off," or "on-off" discharges can be obtained from the same element, depending on many factors, such as background illumination, state of adaptation, intensity and duration of stimulus, and the extent and location of the area which is stimulated within a receptive field. Among these factors the last mentioned seems to be more important in determining the pattern of discharge. Within a small receptive field of retina of 1 to 2 mm. in diameter the discharge pattern of the central region is the opposite to that of the periphery. The center may give predominantly "off" and the periphery "on," or vice versa. The instability of the discharge pattern is interpreted as being due to the interaction of the inhibitory and facilitatory processes in the intraretinal pathways.

All the evidence available now seems to support the view that a rigid classification of mammalian retinal elements in three distinct types is untenable. The large spike potentials recorded by the microelectrode, on the analysis of which the classification is based, are produced by the giant ganglion cells [Rushton (150, 151)]. The origin of the spike potential in the innermost layers where the nerve elements lie has been demonstrated also by Tomita (162) and by Tomita & Funaishi (163). Since the ganglion cells are activated by the receptors through the action of intercalated bipolars and the neural networks, their discharge can not be compared with that of the optic fibers of *Limulus* with which Hartline originally formulated his hypothesis. (There are no synapses between photoreceptors and optic fibers in *Limulus*.)

Electroretinography.—In the field of electroretinography efforts seem to have been mainly concentrated on studying the origin and the functional significance of different components of ERG. Increasing experimental evidences indicate that the *b*-wave of the electroretinogram is associated with rod activity and its pathways as suggested by Granit (60). A large negative deflection following the *b*-wave, which was observed in normal dogs under anesthesia from 3-*o*-toloxy-1,2-propanediol (Myanesin) and pentobarbital (Nembutal), may also be associated with rod activity, since it can be abolished by dark-adaptation and evoked more easily by the light of short than by that of long wave lengths [Parry, Tansley & Thomson (139)]. There was formerly a doubt in regard to the validity of the interpretation, since the ERGs from the blind spot and fovea of the human eye, where rods are absent,

show the same pattern as those from the other parts of the retina with a well-formed *b*-wave constant magnitude independent of changes in the area intensity relationship of the stimulus. However, this result is apparently produced by the stimulation of the whole retina by scattered light [Boynton & Riggs (28)]. Asher (7) also observed the apparently normal ERG from the blind spot and attributed it to the stray lights.

On the basis of the observations that the *b*-wave decreases and the *a*-wave increases with the increase in intensity of the stimulating flickers at moderately low luminance (2000 lux) and that with stimuli of high luminance (24,000 lux) and high frequency the *b*-wave disappears while the fusion of *a*-wave does not occur, Dodt (51) suggests that the appearance of *a*-wave at high intensities is due to cone activity. According to Dodt the human ERG changes from E type to the I type when the eyes are stimulated at high intensities.

Tomita's microelectrode analysis of the intraretinal action potential shows that the *a*-wave changes its polarity when the electrode is traversing the bipolar layer. The PIII is therefore thought to originate in the layer of bipolar cells [Tomita (162)]. But, in another report, the same author seems to favor the view that at least one part of PII and PIII originates in the receptor elements themselves [Tomita & Funaishi (163)].

The characteristics of the frog's ERG produced by stimuli of different wave lengths during dark-adaptation were studied by Müller (130). The *a*-wave was reported to disappear at all wave lengths, and the *b*-wave and the "off" effect became progressively less as the wave length of the stimulus was shortened. Strychnine increased all the components of the ERG, urethane increased and lengthened the *b*-waves, and santonin also increased and lengthened the *b*-waves especially for the blue stimulus. Recently, Armington (4) observed in the electrical response recorded with an electrode mounted in contact lens a characteristic wave called *x*-wave which, according to this author, is associated with red color vision.

A very interesting piece of information about the ontogenetical development of ERG has been obtained from infants by Zeterström (199) who found that in the first few days of human life the retinal potentials are entirely absent and develop gradually during the first six months. By the age of three months the *b*-wave is 0.1 to 0.2 mv., but three months later the *b*-wave is increased to 0.2 to 0.3 mv. The *a*-wave is still absent at the same age. At the age of one year the ERG is of the adult type. The ERG of the baby is characterized by the absence of PIII, which reflects the functional immaturity of certain retinal elements. This observation seems to provide a clue for localizing the origin of different components of retinal action potentials. However, the attempt to correlate the potential components with anatomical structures will not be successful until we fully understand the basic mechanism by which the retinal action potential is produced by light stimulation. From the mathematical relationship between the duration of the light stimulus and the magnitude of the retinal potential developed in the

eyes of the grasshopper or *Limulus*, Wulff & Fry (198) suggest categorically that the underlying mechanism is a series of action and reaction of substances S, C, and P. How these hypothetical substances initiate an electrical change in the retina is left untold.

Another attractive theory concerning the genesis of retinal action potential emerged from the chemical study of the visual purple. As previously mentioned in this review, Wald & Brown (176, 177) demonstrated that during the bleaching of rhodopsin the freeing and binding of sulfhydryl groups were accompanied by electrical variations. They suggested that this phenomenon may have some fundamental connections with the initiation of visual action potentials. Since the —SH groups have strong affinity for positive ions and are apt to make the totality of such groups an effective cathode [Bartlett (10)], the electrical effect observed *in vitro* might have been a mere manifestation of the ionic movement in chemical reactions and is not likely to be simulatory to the process involved in the initiation of the retinal action potential which is known to be a phenomenon of membrane depolarization. But the electrotonic effect may significantly modify the excitability of the sensory and neural elements in the retina so as to favor the initiation of nerve impulses.

Central visual pathways.—An analysis of the electrical response of the visual cortex to stimulation of the optic nerve revealed that the pattern of the response is made up mainly of three independent constituent potentials each consisting of a spike and a slow wave. It is believed that the three spikes represent the synchronous activity of three groups of conducting fibers having three different sizes [Chang & Kaada (38)]. This result is in conformity with the anatomical fact that there are three peaks of distribution lying in the regions of 1μ, 4μ, and 9μ of the fiber caliber spectrum [Chang (35)]. The three groups of fibers according to size are also present in the optic radiation as evidenced by the presence of three spike potentials in the cortical response to geniculate stimulation. By making use of an accidental observation that the cortical response to geniculate stimulation can be enhanced by continuous illumination of retina [Chang (37)], it was further found that the three spike potentials can be selectively potentiated by retinal illumination with monochromatic lights in such a way that the red light enhances predominantly the size of the first spike, the blue light enhances the third, and the green light is somewhat similar to that of the red. From these experiments a conclusion is reached that the impulses for red are transmitted by the fastest fibers, those for blue by the slowest fibers, and those for green probably by the medium sized fibers [Chang (35, 36)].

It seems to be a general principle that the physiological processes underlying the perception of lights of longer wave length are faster than those underlying the perception of lights having shorter wave length. For instance, the maxima of electrical excitability of the retina after a brief illumination with red, green, and blue are reached in 1, 2, and 3 sec. respectively, regardless of light intensity [Motokawa (115, 117)]. The frequency maxima of the

spike discharges of the retina under illumination are likewise reached at different times according to the color used for illumination: the order of efficiency is again found to be red, green, and blue in that sequence [Donner (52)].

However, a different point of view is expressed by Chacko (32) who supports the original thesis of Le Gros Clark (39) that the large fiber system in the central visual pathways is related to blue perception.

The effect of retinal stimulation with lights of different colors in altering the rhythm of the electroencephalograms has been described by Albe-Fessard & Buser (3). The action and interaction of the central visual pathways and especially the geniculostriate system have been analyzed by Marshall (107) and Bishop & Clare (18). The pattern of retinal projection to the cerebral cortex of the rabbit has been mapped by Thompson, Woolsey & Talbot (170).

COLOR THEORIES AND COLOR VISION

Theories of color vision.—A series of papers on color vision presented in the Colour Vision Conference in Cambridge were published in Volume 3 of *Documenta Ophthalmologica*. Of those (27, 39, 61, 69, 74, 90, 92, 97, 105, 144, 145, 155, 184, 195), which embrace almost every aspect of the subject, the most stimulating seems to be the first which summarizes and discusses the present status of the trichromatic theory [Wright (195)]. There is probably not any single subject in the physiology of sense organs which is filled with so many theories as the problem of color vision, and there is not any other theory which has received so much criticism and attack for so many years and yet can still stand solidly unbeaten as the Young-Helmholtz theory of trichromatic vision. A just evaluation of this time-honored theory and other ideas of color vision in the light of recent experimental findings was also admirably made by Thomson (168). Another comprehensive review on color vision was written by Talbot (158) who tends to emphasize the insufficiency of the Young-Helmholtz hypothesis in explaining satisfactorily the facts pertaining to color deficiencies and the phenomena such as complementarity, black, luminosity versus whiteness, adaptive shifts, peripheral color, etc. On the basis of the works of Müller and Adams a modified opponent theory is proposed. According to this theory the color mechanism is mainly operated in the retina by virtue of the specific synaptic arrangements of receptors and neural elements, and many phenomena of color vision may be accounted for in terms of the interplay of impulses between different pathways at the retinal level. On the basis of a tremendous series of experiments designed to test the extent and distribution of individual differences in color vision Pickford (142) favors a modification of Hering's four component theory. In his book *Recent Advances in the Physiology of Vision*, Hartridge (71) proposed a polychromatic theory according to which there are in the retina seven kinds of receptors for the seven distinct visible colors of the spectrum, namely: red, orange, yellow, green, blue-green, blue, and blue-violet [see also Hartridge (69, 72)].

One of the important facts supporting the trichromatic theory of Young-

Helmholtz is the binocular fusion to yellow of red and green, which has been repeatedly demonstrated in recent years [Hecht (74); Gunter (65)]. However, Hurvich & Jameson (86) consider yellow a fundamental color and favor the four-component theory of Hering on the basis of the observation that a pure green and pure red, seen binocularly, do not give the yellow sensation as predicted according to Young-Helmoltz theory. They contend that the yellow synthesizing mechanism operates only when yellow is already present to some degree in the red and green components. According to Talbot (159), Hurvich & Jameson's failure to produce synthetic yellow might have been due to their unfortunate choice of the color components and to the individual variation of their visual apparatus. The evidence presented by them falls short of disproof of the binocular synthesis of yellow. Walls & Mathews (181) also pointed out that the so-called "pure green" color stimulus used by Hurvich & Jameson for obtaining binocular yellow was one which appears blue-green to most normal observers and that according to the ICI[2] chromaticity diagram their wave length mixtures should produce a sensation of purple. The reason why Hurvich & Jameson actually obtained a mental sensation was that they made high level photopic judgement with dark-adapted eyes and with no comparison field [Walls (180)].

An evidence that the yellow process is composed of red and green processes in the central fovea is provided by the studies of Motokawa. From the characteristic manner in which a green color, presented immediately after the cessation of preillumination, inhibits selectively the retinal process of that color, Motokawa found that yellow light was capable of deforming the excitability curves for red and green. However, outside of the fovea yellow seems to be an indivisible single process [Motokawa *et al.* (126)]. The presence in the parafoveal area of a mechanism responding to yellow light is also suggested by Weale (183) but he is not certain whether it is an independent process or a fusion of red and green responses.

Color vision in fovea.—The central fovea of the human eye is said to be physiologically color defective. This defect manifests itself as an inability to distinguish blues from greens. The defective color sensitivity of the central fovea has been intensively studied by Willmer (184 to 190) who, in addition, to confirming his original findings with Wright (191), further demonstrated that the central fovea of subjects with normal vision is tritanopic and the fovea of persons with protanopia and deuteranopia is totally color blind. Thus, normal persons seem to have dichromatic vision and normally dichromatic subjects, monochromatic vision at the fovea. These findings suggest that the assumption of tricolor system is both necessary and adequate to account for the facts of color vision. On theoretical grounds Willmer assumes that the normal subject possesses in the fovea two pathways, A and B, and that the red-green blind possesses either A or B, or possibly both for a limited distance along the neural path which combine before reaching the higher centers. Experimental observations on the normal and color-blind subjects indicate that each of the different groups of subjects has a charac-

teristic luminosity curve as the hypothesis implies, thus, the maximum sensitivity is at 540 mμ for protanopes, at 550 mμ for deuteranopes type I, and at 570 mμ for deuteranopes type II (186). It is also demonstrated that by adapting the fovea to lights of equal brightness from the two ends of the spectrum, the central fovea of the normal subject has its threshold to red and to violet change in a characteristic manner.

Thomson (166) seems to be more conservative in accepting the two-process theory of foveal color vision but inclines to think that the color defect of the central fovea is an inability to distinguish blue and green rather than a blindness to blue. Thomson has meticulously determined both the intensity discrimination at different wave lengths of the central fovea and found that, in the center of the fovea at low brightness, three discrimination maxima remained in the spectral regions of 460 mμ, 520 mμ, and a third between 580 and 610 mμ, corresponding to those for which Granit has found modulator activity (164). It is suggested that at low brightness intensity discrimination is mainly a function of modulators, and at higher brightness is mediated by dominators. The spectral sensitivity curves of the central fovea have been determined by Thomson (166) with a test field subtending 15′ at the eye in five observers, two with normal vision, two with protanopic vision, and one with protanomalous vision. After corrections were made for the absorptions of light by the yellow macular pigment and by hemoglobin, the foveal spectral sensitivity curves were found to have irregular, multi-humped elevations which were apparently concerned with a number of visual mechanisms contributing to color vision. The curves for the protanopes, however, cannot be explained as being a combination of blue and green fundamental curves because of the lack of red receptors. When a test field is enlarged to 1° 20′, the hue discrimination of the central fovea deteriorates at low brightness levels. The deterioration is uniform throughout the spectrum except for the region 420 to 460 mμ, a region in which changes of luminance produce no change of hue discrimination. It can be considered a fact indicating that the eye in a visual field of normal size is not tritanopic at low luminance [Thomson & Trezona (169)].

Color vision outside the fovea.—Under scotopic conditions the chromatic sensitivity of the extrafoveal regions differs markedly from that of the fovea. As demonstrated by Weale (182) the peripheral retina is essentially trichromatic at high brightness levels, but becomes tritanopic when the luminance is reduced. At the highest level of luminance there appear in the regions 10° and 15° two peaks of deterioration in hue discrimination, one at 460 mμ and the other at 590 mμ, suggesting a development of a form of dichromacy which may develop into deuteranopia in more peripheral parts. This result agrees well with that of Gilbert's observation that at high luminance levels the parafoveal color vision does not differ in essential characteristics from foveal vision, but at low illumination color perception becomes reduced to a type of dichromatic vision similar to the tritanopic form of defective color vision [Gilbert (59)]. Brown (29) also found that luminance

levels within the photopic range have little effect on color discrimination, but at low luminance levels a normal observer's vision tends to become tritanomalous.

By measuring the electrical excitability of the eye following a brief illumination with lights of different wave lengths, Motokawa (115) is able to demonstrate the relative spectral sensitivity of different regions of the retina, as follows:

Green > Red > Blue in the fovea
Yellow > Blue > Green > Red at 15° from the fovea
Blue > Yellow > Red > Green at 25° and 35° from the fovea.

The peripheral limit of retina for color sensitivity as determined perimetrically by Baeuml & Engelhardt (8) is 90° to 100° for all colors, 60° for green, and 45° for red. The colors between yellow and red appear as yellow between 90° and 45°, those between green and yellow appear as yellow between approximately 88° and 58°. The colors between red and violet appear as violet between 90° and 85°. The colors between blue and green appear as blue between 90° and 60°.

It is a baffling problem whether all the cones throughout the retina are alike in their functioning as color receptors and, if so, why the color perception in the fovea is different from that in the extrafoveal regions. Concerning this point a recent study by Loevenich (102) deserves attention. From the difference between fovea and parafovea in the resolving power for three wave lengths (650, 600, and 550 mμ) Loevenich suggested that each foveal cone contains all three of the fundamental substances for color vision whereas in the parafovea each cone contains only one of the three substances.

Interaction of color receptors.—The receptors for blue color are mainly rods distributed in the extrafoveal region of the retina, but their activity can be modified by the activity of the other receptors probably through the interaction of their respective pathways. For demonstrating the interaction of rod and cone pathways Willmer (189) devised an experiment in which one-half of the retina is exposed to violet and yellow of sufficiently low intensity ("rod "field), while the other half of the retina is strongly illuminated by the wave band at the red end of the spectrum ("cone" field). He demonstrates that the rod field suddenly darkens, and after a momentary pause appears blue, when the cone field is extinguished, the rod field brightens and its color fades. Willmer (189) has also demonstrated the interaction between different color receptors and their pathways in the central fovea. The activity of a small segregation of red receptors by projection of red light into the central fovea, for instance, depresses the sensitivity of immediately surrounding foveal areas to all spectral colors. The brighter the red field, the greater is the effect it produces. The effect decreases with the distance of the test field from the red field. Although the suppressing effect of red is on all spectral colors, the red receptor seems to suppress the activity of adjacent blue receptors more extensively than it suppresses neighboring red receptors [Will-

mer (188)]. The activity of one kind of color receptors in a particular part of the retina not only affects the subsequent efficiency of the other kinds of receptors in the same area, but also affects the visual process in the neighboring regions of the retina at the same time. The phenomena termed as successive retinal induction and spatial retinal induction, which are apparently intimately connected with various types of optical illusion, have been analyzed by Motokawa by means of his polarization method [Motokawa (116, 120)].

Macular pigment.—The presence of yellow macular pigment in the central fovea of the human retina is obviously a factor affecting the foveal sensitivity to blue. The relatively low luminosity value in the blue end of the spectral luminosity curve for the Egyptians, for instance, is found to be highly correlated with the density of yellow macular pigmentation of this race [Ishak (89)]. But, as pointed out by Thomson (166), the light absorption of the macular pigment is usually overestimated in evaluation of retinal sensitivity.

The real function or even the existence of the macular pigment in the living human eye remains an issue in dispute. According to Dartnall & Thomson (47), the yellow pigment in the macula plays an important role in the respiration of photoreceptors in the fovea where the oxygen supply is likely to be inadequate due to the lack of blood vessels. Denton & Pirenne (48), however, pointed out that the macular pigment cannot play any part in the respiration of photoreceptors, since the pigment is situated in the inner layers of the retina and on the slopes of the fovea. They suggested that the real function of the pigment is likely to reduce disturbances due to chromatic aberration by absorption of blue and violet wave lengths. Both Hartridge (70) and Tansley (161) believe that there is no shortage of oxygen in the fovea, since rods and cones there are supplied from the chorioidal vessels. Apparently influenced by Nordenson's findings (135), Hartridge doubts seriously the existence of macular pigment in the living human eye, and considers the pigment a substance derived from vitamin A, which can be found only post mortem (73).

From the chemical nature of the macular pigment, Ségal (153) suggested that the pigment is made up of products of visual purple bleaching, namely, transient orange and indicator yellow. If this hypothesis is correct, it would tend to support Hartridge's view that the macular pigment could not exist in the living human eye. since the transient orange is a highly thermolabile substance and could not possibly survive at body temperature.

PSYCHOPHYSICAL ASPECTS OF VISION

Threshold phenomena.—Recent findings concerning the threshold of vision are generally in line with the concept that the essential element in producing a sensation of light is the total energy of the stimulus. Long's experiment shows once again that within certain limits the product of intensity and duration of light for threshold of vision is constant [Long (103)]. The

area factor which is not considered in Long's experiment has been studied by Haig (67) who finds that the relationship between area and intensity of the stimulus over a nonhomogeneous portion of the retina can be expressed by a mathematic equation. The variations of contrast thresholds with the size of test area and the intensities of light stimulus were all described by Bouman who found Ricco's law held only when the test field was less than 15′. For large areas Piper's law held better [Bouman (24)].

The two-quantum theory of visual threshold, which states that the absorption of two or more light quanta is necessary for the creation of a sensation of light within a certain time interval and within a certain retinal area, has been favorably discussed and amplified with the support of more experimental evidence by Baumgardt (13) and Bouman (23). Pirenne & Denton (49, 143), however, maintain that the minimal number of quanta needed for vision must be more than two, probably four or more. In a review of Baumgardt's monograph, Stiles (156) pointed out the neural factor which may greatly affect the visual perception but has been ignored by this theory. According to Stiles, the state of facilitation and refractoriness of the receptors following the absorption of the first quantum will determine the effectiveness of the second quantum according to the interval at which the second is delivered.

Curves which relate the probability of seeing a flash of light at the fovea to the intensity of the flash have been determined by Crozier (44) for various wave lengths throughout the visible spectrum. The extensive data can be adequately expressed by a log-Gaussian formulation but not by that based on the conception of Poisson's accumulative distribution which the two-quantum theory finds itself well to fit in. The variation of the seeing frequency value does not seem to depend entirely on the quantal flash fluctuation but rather on the physiological conditions of the organism under test. Mueller (128, 129) found that brightness discrimination cannot be explained on the basis that a fixed number of quanta is required for a discrimination; but his data cannot be satisfactorily described either by Crozier's log-Gaussian integrals or by Poisson's formulations. He considers the quantum theory fundamentally correct and acceptable *mutatus mutandis.*

The relationship between the stimulus area and the threshold of peripheral vision as determined by Riopelle (148) is such that for a given number of spots the threshold always rises as the diameter of the test patch increases and the smaller the spots the greater is the rise in threshold. This is attributed to the dispersion of light and the spatial interaction of the retina. Riopelle & Hake (149) also found that the absolute threshold of human subjects at the region 7.5° inferior to the fovea the lowest and at the region 20° in the same direction the highest.

Opinions are approximate as to the difference in threshold between the central and peripheral regions of the retina. The difference arises from the unequal distribution of rods which, as peripheral photoreceptors, have equal sensitivity regardless of their locations [Matsuura (108)]. A threshold gradi-

ent from the periphery to the fovea, which appears to be correlated with the density of rods, is described by Sloan. But the decrease in cone density between the fovea and the parafoveal parts is much more rapid than the increase in threshold, and the correspondence is completely lacking in the extreme periphery [Sloan (154)].

The absolute threshold for vision in the cat is described as lower than in the humans by a factor of six, which is interpreted as due to the greater speed of animal's dioptric mechanisms and the reflection of the tapetum lucidum [Gunter (64)].

Visual acuity.—The fundamental problems involved in visual acuity has been admirably treated from anatomical, physiological, and optical points of view by O'Brien (136). From anatomical materials of the human eye he found that the center distance between the cones is about 2μ in the fovea but increases rapidly in the parafoveal regions. This cone mosaic is intimately connected with the resolving power of the retina. Optical processes occurring within the cones have been considered and used to explain the Stiles-Crawford effect in a very satisfactory manner. His elucidation of the relationship between visual acuity and retinal structures was based mainly on the observations made under the conditions of the central retina at high level illumination. The changes in acuity of the peripheral retina and at low levels of illumination cannot be accounted for. According to Ogle (137) the resolving power of the human eye as determined by the minimal angle of resolution within certain limits of luminance depends primarily on the contrast, irrespective of the level of adapting luminance. The visual acuity in the peripheral retina is considered by Low (104) as being influenced by the effects of angular eccentricity, nature, brightness and color of the test objects, the limit of viewing time, refractive conditions, spontaneous fluctuations, individual differences, etc. He inclines to believe that the differences between the central and the peripheral acuity are quantitative rather than qualitative. It is, however, a fact that the spherical aberration of the crystalline lens does impair the form perception of the extrafoveal field as demonstrated by Renfrew (147).

An interesting study by Arnulf & Flamant (5) on the relationship between the pupil diameter and visual acuity for different wave lengths should be mentioned here. In this study the authors found that for pupil diameters around 0.2 mm. the resolving power of the eye was better at shorter wave lengths while, for diameters of 2 mm. or over, the wave length has little effect. The relationship of pupil size and visual acuity is complicated by the level of luminance and the refractive conditions of the eye. As demonstrated by Liebowitz (101) there is an optimal size of pupil at which the visual acuity has the maximum value, and above or below which the acuity deteriorates.

The variation of visual acuity with the orientation of the test object relative to the viewing position of the eye is described by Higgins & Stultz (77). They noticed that the visual acuity measured with parallel lines was ap-

preciably lower when the lines were placed at an angle of either 135° or 45° with horizontal than when they were placed either vertically or horizontally. No satisfactory explanation was offered as to the factors producing these variations.

Adaptation.—In the determination of either the threshold or acuity of vision the state of visual adaptation is an important factor affecting the result. One of the most illustrative examples of this is Krieger & Bender's observation that after being dark-adapted the subjects could recognize luminous targets against a dark background in their peripheral retinal areas which are physiologically blind under light-adapted conditions [Krieger & Bender (98)]. Visual adaptation not only affects the threshold and acuity of vision but also affects the subsequent color perception. As observed by Hunt (84, 85), most colors appear much more saturated to the light-adapted eye than to the dark-adapted eye, and changes of hue also occur.

The rate of dark-adaptation seems to depend upon the total quantity of the preadapting light which bleaches the visual purple. After measuring the influence of intermittent versus continuous pre-exposure upon dark adaptation, Mote *et al.* (114) found no difference in subsequent adaptation which could be related to the mode of pre-exposure. In a later paper, however, Mote & Reed (113) indicated that changes in dark-light ratios of the intermittent exposure appeared to have some effects on the threshold and speed of subsequent dark adaptation which may also vary with the intensity of illumination.

The course of dark adaptation of the eyes overexposed to strong light could be markedly prolonged, especially for the eyes with less pigments. It was reported that after exposure to a light of 1000 to 10,000 lux for 1 to 2 hr. the disturbance of sensibility could last for two months after exposure, presumably due to the damaged mechanism of visual purple regeneration [Blystad (20, 21)]. Although the photochemical processes are controlling factors, there has been an increasing tendency not to consider dark-adaptation a purely chemical process related to the regeneration of visual purple. By comparing the speed of sensibility increase for different sized objects during dark adaptation, Best (16) concluded that not only is the synthesis of visual purple responsible for dark adaptation but also the summation of stimuli is important. Thomson (165) also pointed out that simple photochemical scheme is not sufficient to explain the phenomena of dark adaptation. A nervous component located in the retina may be involved. However, no electrical manifestation of the nervous activity correlated with adaptative states has yet been described.

Flicker fusion threshold.—Although the stimulus intensity, retinal position, field size, and adaptation all affect the critical frequency of flicker [McNemar (106)]. The basic determining factor for fusion is apparently the refractory state of the visual mechanism as suggested by the effect of light-dark ratio [Winchell & Simonson (192)]. Best's study on the dependence of the critical frequency of flicker on the size and location of the stimulated

part of retina seems to strengthen this belief. He pointed out differences in fusion frequency between different parts of the retina happened only when the retina was stimulated with light of equal intensity. If the light intensity was adjusted according to the sensitivity gradient of the retina so that each receptor receives equal amount of light, the same critical frequency would be found for various areas because the receptors have equal threshold and latency. Furthermore, the critical frequency of flicker was always higher when a larger area was stimulated, since stimulation of large area shortened the latent period and brought the response to the stimulus more quickly to its height [Best (17)].

The effect of simultaneous brightness contrast on the flicker fusion frequency was reported by Asher (6). He observed that increasing the illumination of the surrounds increased the fusion frequency threshold. This was interpreted as resulting from either the spatial inhibition of the retina or a mutual interaction of the two separate central pathways for the adjacent areas.

The visual area of the cerebral cortex seems to be involved in some way in the mechanism of flicker fusion, since a depression of the fusion frequency is said to occur in the subjects with occipital lobe injuries [Battersby (11)], but not in those with temporal amaurosis or with frontal lobe injuries [Battersby, Bender, & Teuber (12)]. That the central nervous system plays a part in the mechanism of flicker fusion is suggested by the difference in fusion frequency between monocular and binocular stimulation. As demonstrated by Ireland (88) the binocular fusion frequency was significantly higher than the monocular when the testing patches were in phase, and significantly lower when the patches were out of phase, although the fusion frequency for monocular observation was not significantly different for the two eyes. However, this result is not in conformity with the classical study of Sherrington who found no significant difference between monocular and binocular fusion frequencies.

Probably inspired by the potential clinical value of the flicker fusion phenomena, extensive studies have been carried out with a view to finding out the conditions affecting the critical frequency of flicker. It has been found that the variation of fusion frequency may result from room illumination, brightness of test patches [McNemar (106), Fabricant & Murroughs (56)], the action of certain drugs [Landis & Zubin (99)], acid-base changes of blood [Hendly & Alpern (76)], changes in size and mobility of pupil resulting from age [Misiak (111)], the effect of positive acceleration on human centrifuge [Keighley, Clark & Drury (93)], the effect of smoking cigarettes [Fabricant & Rose (55)] or even food intake [Hammer (68)].

Accommodation and convergence.—The role of the accommodative mechanism in the performance of binocular convergence has been discussed by Tait (157). He concluded that the nature and amount of the near point heterophoria which is a prerequisite for binocular convergence depend upon three factors: (*a*) the underlying heterophoria for distance, (*b*) the amount of

accommodation present, and (*c*) the extent to which the accommodative convergence reflex is developed in any individuals. Hofstetter's observation (79) indicates that proximal convergence is closely related, but not definitely correlated, with the amount of fusional convergence in play. The proximal convergence and fusional convergence are believed to have independent neurological orgins.

From the results of experiments with alternate haploscopic stimulation of both retinae, Winkelman (193) postulated a theory concerning binocular optic reflexes. According to this theory the sensory and motor impulses initiated by the retinal activity are responsible for a series of reactions leading to the binocular convergence in stereoscopic vision. This theory implies the importance of an ocular scanning process in binocular vision which Adamson (2) has maintained. According to Adamson the association of stereoscopic sensation with retinal disparity holds only for the fovea. In the extrafoveal regions the space perception is achieved largely by scanning of the visual field of the eyes. Wright (196), however, demonstrated that under ordinary conditions small eye movements are not necessary for fusion and do not enhance stereoscopic perception. The ability of the peripheral visual apparatus to bring the focus of the image on the retina is a process involving delicate reflexes. According to Fincham (57) two factors are concerned in stimulating the accommodation reflex: chromatic aberration of the eye lens and the minute rotation of the visual axis or scanning, both of which have been generally regarded as natural defects of the eyes. When there is no external stimulus to put the accommodation reflex in action, the position taken by the resting eye lens is not focused to infinity, as one may have believed, but to a distance of about 0.8 m. [Otero (138)]. The dysfunction of the accommodative mechanism in dim light is believed to be intimately related to night myopia, the near-sightedness of the normal eye in dim light which may amount to a value as high as 1.5 to 2.0 diopters. Koomen *et al.* (94), however, believe that the spherical aberration combined with the dilation of the pupil of the observer's eyes in dim light constitutes the main cause of night myopia. They proved that night myopia appeared even when accommodation was prevented by an optical method or paralyzed by homatropine. Bouman & van der Brink's results also indicate that night myopia is partly due to spherical aberration (26).

In ophthalmological practice it has been believed that a slight fogging of the vision of the nondominant eye can give the dominant eye better acuity. Jacques (91) challenges the correctness of this belief and claims that the best results can be obtained when the patient is corrected so as to give him the best acuity of each eye, i.e., fully corrected for his ametropia and anisometropia. This provides for the accommodative efforts of the two eyes to be exactly equal which leads to the relief from strain and to better vision.

It is a traditional concept that binocular vision depends on corresponding images in the two retinae. These two images are by no means identical in form because of the inevitable difference in angle of viewing between the

two eyes. This retinal disparity is considered as important data for mental analysis and synthesis in order to produce three-dimensional perception [Wright (196)]. Other factors contributing to the stereoscopic appreciation of space include accommodation convergence, visual acuity, and subsidiary clues [Colson (43)], the relative importance of which seem to vary with various conditions. In a discussion of stereopsis, Burian (31) emphasizes the importance of the process of central fusion of disparate images, and accordingly he regards the stereopsis as a visual sensation in its own right, independent of other related visual processes.

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THE ANTERIOR PITUITARY AND ADRENAL CORTEX[1]

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The past year has again been marked by intense activity and interest in the field of pituitary and adrenal physiology, and hence it has been possible to review here only a portion of the many interesting contributions in this field. The review covers the period from June, 1951 to July, 1952 for ACTH[1] and the adrenal cortex, and from June, 1950 to July, 1952 in the case of the anterior pituitary since the latter was not covered in Volume 14 of the *Annual Review of Physiology.*

Chemistry, Physical Properties and Metabolism of ACTH and Adrenal Steroids

Limitations of space prevent a detailed review of the many interesting papers that have appeared during the last year in this rapidly expanding field. Application of increasingly ingenious chemical and physical methods has characterized this work. Excellent reviews on the chemistry of ACTH have been published by Astwood *et al.* (1) and Dedman *et al.* (2), and on the biosynthesis of adrenal steroids by Hechter *et al.* (3) and Haines (4). British investigators have summarized experiences with methods of bioassay of ACTH and adrenal steroids (5 to 9).

ACTH.[1]—Active preparations of ACTH from sheep and horse pituitaries have been isolated by a simplified procedure by Li *et al.* (10, 11), while Smith *et al.* (12) describe a simple technique for isolation of ACTH using an acid-acetone extraction with lithium chloride to promote solubility of the ACTH. Raben *et al.* (13) outline steps for the separation of other pituitary hormones from ACTH prepared by the oxycellulose adsorption method. Centrifugation of frozen hog pituitaries at 25,000 g. at 1° to 5° C. yields an exudate with extremely high ACTH activity which is recommended by Munson & Miley (14) as a useful starting material for purification of the hormone in its native state. The stability of ACTH in acid solutions is confirmed (15) while its instability in neutral aqueous extracts is believed to be due only in part to destruction by proteolytic enzyme, pre-

[1] The following abbreviations are used in this text: ACTH (adrenocorticotropin); ATP (adenosinetriphosphate); DCA (desoxycorticosterone acetate); ADHA (alloxan-diabetic-hypophysectomized-adrenalectomized; SKF-501 (N-[9-Fluorenyl]-N-Ethyl-β chloroethylamine hydrochloride).

[2] This work was done during the tenure of a grant from the American Cancer Society, administered by the Committee on Growth of the National Research Council. The author is indebted to Dr. W. S. Lynn for aid in surveying the literature and to Miss Rose Ina Weeks for secretarial and bibliographical assistance.

sumably by the enzymes described by Adams & Smith (16) as occurring in pituitary extracts.

The problem of the precise chemical nature of ACTH[1] still eludes solution. Data reviewed by Astwood (1) and Morris (2), however, lead to the conclusion that ACTH is a small molecule, with basic properties, containing one or more peptide bonds, but probably no free amino groups, although amino and carboxyl groups appear to be essential for its activity. However, until an undisputably chemically pure ACTH is prepared, uncertainties will continue to exist as to whether chemical and physical properties ascribed to the hormone are truly those of the hormone or of contaminants carried with it in the purification process. Chromatographic methods, using different adsorbants and eluants, have proven particularly useful in the so far incompletely successful attempts to separate and characterize pituitary fractions with ACTH activity (1, 2, 17 to 20).

Chemical separations of the type noted above plus evaluation of bioassay methods suggest the possibility that there are two types of ACTH[1] in the pituitary, one active in its ability to deplete adrenal ascorbic acid and the other effecting adrenal repair in hypophysectomized animals. While there is general agreement among all those who have studied this problem that there may be considerable discrepancy in results of the adrenal repair and ascorbic acid assays in response to different pituitary extracts and purified preparations of ACTH (1, 2, 7, 19, 21 to 24), it should be recognized, as emphasized by Astwood (1) and Reinhardt *et al.* (22), that these differences cannot be taken as unequivocal evidence of a multiplicity of ACTH factors. Variations in the route of administration, differences in the rate of absorption of preparations made by different methods, and differential time response relationships for ascorbic acid depletion and repair may all play significant roles in determining the results of various types of assays. Ingle & Li (25) found an ACTH protein preparation given by continuous subcutaneous injection to be about twice as active in inducing signs of hypercorticalism as an ACTH peptide similarly administered, although the peptide was more potent in causing ascorbic acid depletion of the adrenal cortex. Alum precipitation of ACTH protein increased its ability to cause adrenal hypertrophy and thymus involution, but an alum-precipated ACTH peptide caused thymus involution, but not adrenal hypertrophy, the peptide alone having no effect on either process (26). The authors' conclusion that thymus involution is a more sensitive indicator of ACTH activity than adrenal hypertrophy must be accepted with reservations, in view of Selye's claim that certain ACTH preparations produce thymolysis in cortisone-maintained adrenalectomized rats (27, 28).[3]

[3] Bush & Stack-Dunne (315) by measuring the steroid content of adrenal vein blood of hypophysectomized rats following intravenous injection of the ascorbic acid depleting factor and the adrenal weight factor respectively have presented evidence that the two are distinct and have different actions independent of absorption rates. Twenty-four hours after hypophysectomy, the adrenal ascorbic acid factor increased

ACTH[1] incubated with liver tissue *in vitro* was inactivated (29, 30). Boiled liver tissue was less effective (30). Intrasplenic injection (29) or oral administration of ACTH (31) resulted in adrenal ascorbic acid depletion in hypophysectomized rats, but the dose effective orally was 4000 times the effective intravenous dose. Injected ACTH accumulates to a considerable degree in kidney (31).

Several methods have now been described for the determination of ACTH in blood (32 to 36). Opsahl & Long (37) present evidence for the presence of ACTH in human placental tissue.

The claim is made by Sulman (38, 39) and Johnsson & Hogberg (40) that intermedin and ACTH are closely related or identical chemically since they were unable to separate the two, and they found a close correlation between melanophoric and ascorbic acid depleting activity of ACTH preparations. However, Raben *et al.* (13) and Geschwind *et al.* (40a) have succeeded in effecting a separation of intermedin from ACTH. The latter investigators were unable to demonstrate any correlation between ascorbic acid depleting and melanophoric activity of ACTH preparations. However, they did note that the pars intermedia of frog pituitaries contained significant amounts of ACTH. Thus, while the two hormones appear to be separate entities, there may still be a functional relationship between them since evidence of elevated blood levels of intermedin is found in Addison's disease (40, 41), after stress (40) and during pregnancy (42).

Adrenal steroids.—The reader is referred to the two excellent reviews on the biosynthesis of adrenal steroids by Hechter *et al.* (3) and Haines (4) for an up-to-date summary of progress in this field. By the use of the techniques of adrenal perfusion and of incubation of various substrates with adrenal slices and homogenates, these and other investigators have now established with reasonable certainty that the adrenal cortex possesses enzyme systems which catalyze C-11, C-17, and C-21 hydroxylation of the steroid nucleus (3, 4, 43, 44). Hayano & Dorfman have shown that ATP[1], fumarate, malate, succinate, and magnesium ion stimulate the hydroxylation at C-11 (45, 46). Corticosterone and 17-hydroxycorticosterone appear to be the main steroids formed by the adrenal cortex. Studies with C^{14}-labeled acetate and cholesterol indicate that these adrenal steroids may be derived from either acetate or cholesterol, but that cholesterol is not an obligatory intermediate in corticosteroid synthesis from acetate. Conversely, cholesterol is not degraded to acetate before synthesis to corticosteroids (3, 4, 47). Haynes *et al.* (48) found that more C^{14}-labeled 17-hydroxycorticosterone was formed from C^{14} acetate in adrenal slices incubated with ACTH (Astwood) than in

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the corticosterone content of the adrenal vein while the adrenal weight factor had no effect on corticosterone secretion. One week after hypophysectomy, there was no acute secretory response to either factor even if the animal was previously treated with the adrenal weight factor, but a high rate of corticosterone secretion could be maintained during this period by the adrenal ascorbic acid factor in beeswax.

slices not so incubated. Corticosterone and 17-hydroxycorticosterone have been identified in adrenal vein blood of dogs (4, 49), corticosterone but not hydroxycorticosterone in adrenal vein blood from stressed rats (50), and a fraction with androgenic activity and a positive reaction for 17-ketosteroids in the adrenal vein blood of cows (51). Plasma dialysates obtained from dogs by the artificial kidney or peritoneal lavage have been found by Savard *et al.* (52) to contain corticosteroids (probably Compounds F and B) part of which were in a free, lipid-soluble state and part in a water-soluble, lipid-insoluble state which could be made lipid-soluble with the aid of β-glucuronidase. Certain of the corticosteroids were found to be associated with the β-lipoprotein fraction of serum.

Nelson & Samuels (53) present a method for determination of 17-hydroxycorticosterone in peripheral blood. Using this technique in the dog, Nelson & Harding (54) demonstrated that intravenously infused 17-hydroxycorticosterone is rapidly removed by the liver, as indicated by large arterial-hepatic vein differences in steroid concentration. Louchart & Jailer (55) find cortisone to be inactivated by liver slices *in vitro*. Inactivation of cortisone *in vivo* does not occur, since Read (56) could find no evidence of adrenal cortical insufficiency in adrenalectomized rats with adrenal transplants in the spleen. Grundy, Simpson & Tait (57, 58) announce the isolation from beef adrenal extract of a steroid with 20 times the activity of DCA[1] in mineral metabolism. Its structure has not been elucidated but they suggest it might be Reichstein's Compound R (allopregnane-3β, 11, 21-triol-20-one) or an epimer thereof. Zaffaroni *et al.* (59, 60) report on the application of the technique of filter paper chromatography to the characterization of corticosteroids in beef adrenal extract and normal urine. In the latter case, Compounds F and E were identified but not desoxycorticosterone. Other studies have shown the presence of these same compounds as well as tetrahydrocortisone and tetrahydro-hydrocortisone in normal urine as well as in urines of subjects receiving ACTH (61 to 63). A number of new modifications of existing methods of analysis of corticosteroids are described (64 to 70). ACTH treatment increases the excretion of urinary dehydroisoandrosterone (71). Urinary dehydroisoandrosterone levels were found to be high in two cases of virilizing adrenal tumor, but normal in adrenal hyperplasia. Cortisone did not decrease dehydroisoandrosterone excretion in the urine of patients with virilizing adrenal tumors (72).

Recent reports on the oxidative metabolism of adrenal slices and homogenates and on the adrenal activity of pantothenic acid-deficient rats have bearing on the studies on biosynthesis of adrenal steroids discussed above. Sourkes & Henaege (73) find beef adrenal to be qualitatively similar to other tissues with regard to the use of Krebs cycle intermediaries, a finding consistent with Hayano & Dorfman's observations noted above on the substrate requirements for C-11 hydroxylation of steroids (45, 46). Sourkes & Henaege (74) also report that the adrenals of cortisone-treated rats show a decreased endogenous respiration and oxidation of Krebs cycle intermedi-

aries. Succinic dehydrogenase activity of adrenal homogenates measured by the tetrazolium technique is increased by ACTH and cold stress and decreased by cortisone treatment (75). Winters *et al.* (76, 77) and Hurley & Morgan (78) present convincing evidence of adrenal insufficiency and unresponsiveness to stimulation by ACTH and stress (low oxygen tension) in the pantothenic acid-deficient rat as indicated by the lymphocyte and eosinophil counts and blood sugar and liver glycogen levels. The deficient rats responded normally to adrenal extract or cortisone but not to ACTH or stress, thus localizing the cause of the adrenal failure during pantothenic acid deficiency in the secretory ability of the adrenal cortex itself. These results are of considerable interest in the light of current knowledge of the role of pantothenic acid and coenzyme A in acetate metabolism and the data recorded above concerning the utilization of acetate in biosynthesis of adrenal steroids.

Adrenal Cortex and Intermediary Metabolism

Nitrogen metabolism.—Recent studies on body composition and nitrogen balance have extended knowledge concerning the growth inhibiting response to adrenal hormone overdosage. Kochakian & Robertson (79, 80) have reported on the effects of implantation of pellets of several different corticoids on nitrogen balance, body composition, and organ weights in castrated mice. Cortisone acetate induced a rapid loss of weight, an increase in nitrogen excretion, and loss of carcass protein and water for the first seven days. Thereafter, both weight and positive nitrogen balance were restored, and no further carcass protein was lost. This coincided with a spontaneous increase in food intake. A similar positive nitrogen balance was noted by Pearson & Eliel (81) in a patient with a lymphoma being treated with ACTH when he was allowed to satisfy his appetite by increasing his food intake. It is conceivable that the stimulation of appetite noted during ACTH or cortisone treatment may represent an adaptation by the organism to protect itself against undue nitrogen loss. Metabolic adaptation to adrenal hormone overdosage occurs by other mechanisms: Ingle and co-workers (82, 83) have noted in tube-fed rats that the negative nitrogen balance, resulting from continuous injection of ACTH or large doses of cortisone acetate, likewise decreases after several days, the diet and dose of hormone being kept constant. With larger doses of hormone, the magnitude and duration of the nitrogen loss are greater, indicating that the adaptation is not simply due to depletion of some readily mobilizable protein. Kochakian & Robertson's data (79) suggested that the early stage of rapid nitrogen loss can be correlated with the phase of maximal involution of lymphoid tissue. The possibility that nutritional factors are involved in both the rapid phase of nitrogen loss and the subsequent adaptation must be considered, in view of the report of Meites (84) that pyridoxine and aureomycin will prevent the thymic involution and inhibition of growth seen in cortisone-treated, pyridoxine-deficient rats.

Maassen (85 to 87) has presented data indicating that adrenalectomized rats grow more rapidly than pair-fed controls when body weight, tail length, and width of the tibial epiphyses are used as criteria of growth. The greater growth capacity in the absence of the adrenals was found to an even greater degree in alloxan diabetic animals, a not unexpected finding since adrenalectomy alleviates diabetes which itself inhibits growth. Growth hormone stimulated more growth in hypophysectomized-adrenalectomized animals receiving ACTH than in pair-fed hypophysectomized rats similarly treated. DCA inhibited body and tail growth in normal young rats (87). Baker & Miller (88) noted a depression of serum albumin in adrenalectomized and "panendocrinectomized" dogs. Albumin levels could be restored by treatment with 100 mg. of cortisone daily for seven days. Roberts (89), continuing his studies on protein transformation *in vitro*, reported that the release of α-globulin and utilization of albumin by liver and lymphoid minces were under adrenal cortical control, adrenalectomy depressing albumin utilization and globulin release and hormone treatment accentuating them. Novak (90) reports the unexpected finding that C^{14}-labeled histidine was incorporated into the tissue proteins of adult mice at a greater rate, and also oxidized more rapidly in ACTH-treated animals than in controls. One wonders whether the ACTH used in these experiments was contaminated with growth hormone.

Engel (91), continuing his studies on the role of the adrenal cortex in the metabolism of amino acids in nephrectomized animals, has modified his earlier view that the adrenal cortex exerts little influence on amino acid metabolism compared to that on protein metabolism. He now finds that if amino acids are injected intravenously in 20 per cent glucose, less urea is formed in adrenalectomized-nephrectomized rats than in similarly treated nephrectomized rats. Without accompanying glucose, amino acids are converted to urea equally by both groups of animals. Twenty per cent glucose significantly decreased urea formation from injected amino acids in control nephrectomized rats, but not in ACTH-treated nephrectomized rats. These results favor the view that some of the observed effects of the adrenal hormone on amino acid metabolism may be secondary to altered rates of some steps in carbohydrate metabolism.

Other investigators have presented further evidence for a role of the adrenal in amino acid metabolism *in vivo* and *in vitro*. Umbreit & Tonhazy (92) and Kuriaki & Kensler (93) confirmed an earlier report (94) of decreased D-amino acid oxidase activity in the liver but not the kidney of adrenalectomized rats. The lowered enzyme activity could be restored to normal by cortisone treatment of the rat (92). The loss in activity was found in the mitochondrial fraction (93). Proline oxidation is decreased in kidney slices and homogenates, but not in the liver of adrenalectomized rats (95). The difference in proline oxidation becomes apparent 2 to 3 days after adrenalectomy and can be prevented by pretreatment with cortisone, but as much as a week of treatment is necessary to restore enzyme activity to normal after

adrenalectomy. Porter *et al.* (96) describe a decreased urinary excretion of kynurenic acid after injection of L-tryptophan into adrenalectomized rats. Cortisone prevents the decrease in kynurenic acid excretion in adrenalectomized rats and increases it in normal rats. Neither xanthurenic acid or kynurenine excretion is affected. A related finding is that of Knox (97) who reports that the tryptophan peroxidase activity of rat liver is rapidly increased after various nonspecific, stress-inducing agents, including histamine and epinephrine, in normal but not in adrenalectomized rats.

Engel & Schwartz (98) were unable to demonstrate any effect of ACTH on the peptidase activity of crude extracts of liver, muscle, skin, spleen, lung, and kidney of rats. Cullen *et al.* (99) and Hohansen & Thygesen (100) confirmed an earlier report (101) that the elevated serum peptidase activity found in a variety of pathological conditions may be restored to normal by ACTH or cortisone treatment but only when concomitant clinical improvement likewise occurs. The action of adrenal hormone in this regard is thus nonspecific.

Carbohydrate metabolism.—In extension of earlier studies, Ingle *et al.* (82, 83) have found that continuous subcutaneous administration of ACTH up to 21 days or intramuscular cortisone in excess of 5 mg. daily caused glycosuria and acetonuria in rats force-fed on a high fat, low carbohydrate diet. Five mg. of cortisone induced glycosuria without acetonuria in rats on a medium carbohydrate diet. Lazarow (102) reports that glutathione injected intraperitoneally aggravated the diabetes induced by cortisone, hydrocortisone, or ACTH in rats force-fed a medium carbohydrate diet. This finding is at variance with that of Conn *et al.* (103) who noted alleviation of steroid diabetes by glutathione in man. Both groups of investigators described a fall in blood glutathione levels in steroid diabetes. Grunert & Phillips (104), on the other hand, failed to detect any alteration in blood glutathione after single or multiple injections of ACTH or following histamine, epinephrine, or cold stress in the rat. The mechanism for the diabetes-potentiating effect of glutathione in Lazarow's studies is not apparent. The possibility that glutathione might activate a sulphydryl enzyme, such as phosphorylase, is suggested. Appel *et al.* (105) describe a significant impairment in insulin tolerance of patients after 4 hr. of intravenous infusion of ACTH.

Villee, White & Hastings (106) have carried out a detailed study on the *in vitro* metabolism of C^{14}-labeled glucose and pyruvate by the isolated diaphragms of normal, alloxan diabetic, and adrenalectomized rats, including observations on the effects of insulin. In the diaphragms of all three types of animals, the addition of insulin increased glucose utilization, glycogen synthesis, and the amount of glucose converted to CO_2. Insulin had no effect on pyruvate utilization in diaphragms from normal or adrenalectomized rats, but restored to normal the low pyruvate utilization noted in diabetic diaphragms. Muscle from adrenalectomized rats synthesized less glycogen than normal, but a greater than normal proportion of glycogen was derived from

glucose. It was suggested that this might represent an effect of the absence of the adrenals on the conversion of glucose-6-phosphate to glycogen. Diaphragms from adrenalectomized rats exhibited a decreased production of lactic acid from pyruvate, but the conversion of pyruvate to CO_2 was normal. When carbon balances were caclulated in normal diaphragms exposed to insulin, 85 per cent of the carbon could be accounted for as glucose and pyruvate utilization, lactate formation, and glycogen and CO_2 production, while only 50 per cent could be so accounted for in insulin-treated diaphragms from adrenalectomized rats. Apparently, differences exist in the other pathways of utilization of the carbon, such as conversion to fat and protein. Wick, Drury & MacKay (107) were unable to demonstrate any effect of either adrenalectomy or adrenal cortical extract on the oxidation of C^{14} glucose to CO_2 when C^{14} glucose was infused into eviscerate rats.

Martin and co-workers (108) are studying the effect of adrenal steroids on human leukocyte metabolism *in vitro*. They find that 10 μg. of either cortisone or hydrocortisone per ml. of cell suspension decreases lactate production and glucose utilization but has no effect on oxygen consumption. Cell injury induced by various bacterial endotoxins depresses oxygen consumption and increases glucose utilization and lactate production. Cortisone or hydrocortisone, added to the cell suspension 3 hr. before toxins, completely inhibits the metabolic consequences of injury. These studies have important implications in the interpretation of some of the therapeutic effects of these hormones.

Serum citric acid levels in rabbits are reported to fall 4 hr. after injection of cortisone and, paradoxically, to rise following a single injection of ACTH (109). Cortisone acetate had no inhibitory effect on tissue citrate synthesis in fluoracetate-poisoned rats (110). Long (111) has reviewed the endocrine control of the blood sugar. Ingle (112) reports that adrenalectomized rats exhibit a greater weight loss, glycosuria, and incidence of pathological changes, such as ulceration of the gastrointestinal tract and infection, when treated with large doses of cortisone, than do intact rats.

Fat metabolism.—The precise role of adrenal hormones in fat metabolism remains controversial. Brady, Lukens & Gurin (113) described a profound inhibition of fatty acid synthesis from C^{14}-labeled acetate in liver slices from rats treated with cortisone for three days. Balmain, Folley & Glascock (114) noted a similar depression of fatty acid synthesis from C^{14} acetate and C^{14} glucose in rat mammary gland slices, incubated with cortisone *in vitro*. In the latter case, the inhibition could be overcome by the addition of insulin to the medium, insulin alone having a stimulating effect on lipogenesis. These results are consistent with earlier ones of Welt & Wilhelmi (115) who reported that ACTH decreased the incorporation of deuterium into fatty acids *in vivo*, while adrenalectomy produced an increased incorporation. Altman, Miller & Bly (116), on the other hand, found that perfusion of rat livers with heparinized blood, to which was added C^{14}-labeled acetate and 500 mg. of glucose, resulted in no change in triglyceride or phospholipid fatty

acid synthesis when cortisone was added to the perfusion mixture. A considerable stimulation of lipogenesis was noted when insulin was added and a striking increase seen when both insulin and cortisone were present. On the other hand, cortisone perfusion caused a two-fold increase in the incorporation of acetate into cholesterol, insulin and cortisone plus insulin having no effects on this process. Another example of an apparent synergism between cortisone and insulin in fat metabolism is found in reports of Engel & Scott (117, 118). They state that cortisone and ACTH, as well as cold stress, have no effect on glycogen accumulation in adipose tissue, but markedly potentiate the stimulating effect of insulin on the glycogen concentration of adipose tissue in the fasted rat. The precise significance of adipose tissue glycogen in relation to lipogenesis remains unclarified, however.

Opinions concerning the role of the adrenal cortex in ketone metabolism are also in a state of flux. Under question is the commonly accepted notion that adrenal hormones stimulate ketosis and adrenalectomy suppresses it. Thus, Kinsell *et al.* (119, 120) describe a suppression of fasting ketosis in man by either ACTH or cortisone therapy. The effect seemingly was due to inhibition of ketone body formation, since lower levels of blood ketone bodies resulted after infusion of sodium octanoate in cortisone-treated individuals than in normals. Scott & Engel (121) and Engel & Engel (122) have likewise demonstrated an inhibitory effect of cortisone and hydrocortisone on fasting ketosis in rats. The former have shown in addition that the ketosis associated with cold stress also can be suppressed by these steroids. The paradoxical finding that ACTH stimulates ketosis has been explained by the demonstration that ACTH is equally effective in the cortisone-maintained adrenalectomized rat, indicating that this is either an extra-adrenal effect of ACTH or, more likely, available preparations of ACTH are contaminated with a ketogenic factor (122). Ketosis in dairy cattle can be effectively treated with ACTH or cortisone (123). In seeming contrast to these results is that of Segaloff & Many (124) who report that various 11-oxygenated steroids increase ketone excretion of fasting phloridzinized adrenalectomized rats above that of intact controls. Since blood ketone levels were not measured, and untreated adrenalectomized rats were not maintained with saline, one cannot attach much significance to the complete suppression of ketone excretion in the absence of the adrenals in this study. The increases in urinary ketone excretion to the level in intact controls, following treatment of adrenalectomized rats with various steroids, might be attributed in part to improvement in renal function as well as to metabolic effects of the steroids. In point of fact, examination of the data indicates that an increase in ketonuria above normal occurred only after a low dose of hog adrenal extract, larger doses resulting in lower excretion again. Compounds A acetate, B, and F restored ketone excretion to normal, while with cortisone and cortisone acetate ketone excretion was low at all dose levels. ACTH in a total dose up to 40 mg. injected every 6 hr. stimulated the greatest ketosis and glucosuria in intact phloridzinized rats, but, significantly, nitrogen excretion was suppressed to

below the controls at all dose levels of ACTH used. The latter finding suggests that growth hormone or some closely related factor from the pituitary contaminating the ACTH was responsible for the ketosis (122). However, the controversy concerning the role of the adrenals in ketone metabolism is not readily resolved when one recalls that Ingle *et al.* (82, 83) described ketonuria and glycosuria in rats force-fed a high fat diet and treated with large doses of cortisone or continuous subcutaneous infusion of ACTH. In addition and in confirmation of earlier reports, Lipsett & Moore (125) have found that ketone body production was significantly decreased in liver slices from 20-hr. fasted, saline-maintained, adrenalectomized mice, and could be restored to normal by the administration of 0.1 mg. of cortisone. As is noted elsewhere in the discussion of the role of anterior pituitary factors in ketone metabolism, it is likely that a certain amount of adrenal hormone may be necessary for ketogenesis to occur in response to various stimuli. Overdosage of adrenal steroids seemingly has an opposite effect.

Bloom & Pierce (126) were unable to detect any change in total serum cholesterol or in the S_f 10 to 20 class of lipoproteins during prolonged treatment of patients with cortisone. In another report (127), however, they found that in the rabbit large quantities of serum lipoproteins of the 80 to 400 class and lesser amounts of S_f 40 to 80 lipoproteins appeared after three or four days of cortisone treatment. No lipoproteins below S_f 20 could be demonstrated after treatment, suggesting that a metabolic block at the level of the S_f 40 to 80 class occurred. On stopping therapy, serial conversion of S_f 80 to 400 lipoproteins to those lower S_f values took place until the normally occurring S_f 3 to 12 class was reached.

Enzymes in vitro.—After adrenalectomy in the rat, Umbreit & Tonhazy (128) have found an increase in factors causing the destruction of enzyme activity in isotonic kidney homogenates. After addition of adenylate or NaF, oxidation of glutamate, α-ketoglutarate, succinate, fumarate, and citrate became normal, but proline oxidation remained low in homogenates from adrenalectomized animals. New reports have appeared on the effects of adrenalectomy and corticoids on arginase activity of various tissues (129), on liver catalase (130), lymph histaminase (131), liver succinoxidase (132), and β-glucuronidase activity of the female reproductive tract (133). Several reviews on the adrenal cortex and enzymes have been published (134, 135, 136).

Electrolyte and water metabolism.—Roberts & Pitts (137) report that both cortisone acetate and DCA administered intravenously decrease urinary excretion of sodium and chloride during the subsequent 2 to 3 hr. in adrenalectomized dogs previously maintained on saline. When injected together, the hormones had an additive effect. In contrast with these acute effects of cortisone, Davis, Bass & Overman (138) and Barlow *et al.* (139) describe urinary loss of sodium and chloride, lowering of serum Cl and Na levels, and an antagonistic effect of DCA and cortisone in radio-sodium transport (140) when these hormones were administered to adrenalectomized dogs over ex-

tended periods. Significantly, in terms of the ability of the cortisone-maintained, adrenalectomized animals to withstand stress, these dogs were kept in apparently normal health, with normal blood pressure and hemoglobin for weeks with serum sodium values below 120 m.eq./l (139).[4] This latter finding is of great importance in terms of the effect of hyponatremia on survival after adrenalectomy. Apparently, cortisone confers on the organism a normal ability to resist the stress of salt loss as effectively as it enables the adrenalectomized organism to adapt to other stressful situations. Rosenbaum *et al.* (141) were able to abolish or reverse the diurnal variation in excretion of sodium, chloride, and water in man with cortisone but not with DCA. They present evidence that this effect of cortisone is not a direct one on renal function but is mediated by some other mechanism, possibly through the central nervous system. These same investigators confirmed the observation of others that sodium retention may occur initially on cortisone therapy but frequently disappears or is replaced by sodium loss on continued treatment. All the above studies make it very apparent that the action of cortisone in electrolyte metabolism is very complex and still needs to be elucidated. A method for the bioassay of mineral activity of corticosteroids based on the depression of the urinary Na^{24}/K^{42} ratio in adrenalectomized rats is described by Simpson & Tait (142), and one depending on urinary sodium and potassium excretion after a sodium load in adrenalectomized rats is reported by Marcus *et al.* (142a).

Gaunt (143) and Lloyd (144) have reviewed their interesting research on the adrenal cortex and water metabolism with its implications concerning a functional interrelationship between 11-oxysteroids and an antidiuretic substance, possibly of posterior pituitary origin, in the control of water excretion by the kidney. Slessor (145), using comparable techniques, has confirmed Lloyd's results by finding increased levels of an antidiuretic substance in the blood and urine of patients with Addison's disease. Treatment with cortisone restored the normal response to a water load and reduced the antidiuretic activity of the serum of the patient with Addison's disease. Ames & Van Dyke (146) rather seriously criticize the Birnie technique (147) for assay of antidiuretic substance in serum used by the above investigators, and fail to confirm their claim that the levels of antidiuretic substances are elevated in the serum of adrenalectomized rats when they used a more sensitive technique of assay as well as the Birnie method. Frost & Talmage (148, 149) present evidence that, both in the presence and absence of the kidneys, a larger proportion of an orally administered water load is shifted to an intracellular site in adrenalectomized rats than in normal rats.

Miscellaneous Observations on the Adrenal Cortex

Tissue and cell responses.—Thoracic duct lymphocytes respond to hypoph-

[4] In a more recent report these same investigators find larger doses of cortisone will effectively and indefinitely prevent salt loss and hyponatremia and hypochloremia in adrenalectomized dogs (314).

ysectomy, adrenalectomy, and to ACTH and epinephrine administration in a manner quite comparable to those in peripheral blood (150). The increased ability of the fixed macrophagic cell of the spleen to take up thorium during chronic dietary restriction appears to be under pituitary-adrenal control (151). Cavallero & Braccini (152) describe a reduction in mast cell counts of skin, muscle, and myocardial tissue in cortisone-treated rats and relate this to a decrease in hyaluronic content of connective tissue. Layton's report (153) of an inhibitory effect of cortisone on chondroitin sulfate synthesis by embryonic and wound tissues is of particular interest in this regard. The retarding effect of cortisone on granulation tissue and wound healing is, of course, well established and has been even suggested as a basis for bioassay of ACTH (8, 154).

Both inflammatory and foreign body reactions are considerably modified by cortisone compared to the reaction to a cholesterol pellet or a foreign body (155). Baker also found suppression of mononuclear macrophage infiltration and their fusion to form giant cells and inhibition of capillary growth in the region of a cortisone pellet. Others have found suppression of almost all elements of the inflammatory response to physical and chemical agents, bacterial products, and allergens (156 to 161). Necrosis is not prevented and the tendency to bacterial invasion at the site of injury is increased because of the lowering of the inflammatory barrier (162). Thomas & Good (163) present convincing evidence that the local barrier to bacterial toxins is likewise reduced by ACTH or cortisone treatment, probably by interference with the protective action of the reticuloendothelial system (164). Spontaneous and acquired infections with organisms to which the host is not ordinarily considered particularly susceptible is being seen with increasing frequency in hormone-treated subjects, as exemplified by LeMaistre & Tompsett's report of pseudotuberculosis infection (165) and Lemonde's report of infection with mycobacterium tuberculosis in cortisone treated rats (166).

Hayes *et al.* (167, 168) describe two effects of adrenal extract on the spreading action of hyaluronidase. Acute administration produces the previously described inhibitory effect on hyaluronidase spreading, while chronic administration induces a marked increase in the rate and extent of spreading as well as an alteration in the pattern of spreading. They attribute the second effect to an alteration in the ground substance, an interpretation consistent with Layton's demonstration of an inhibitory effect of cortisone on chondroitin sulfate synthesis (153). Winter & Flataker (169) likewise present evidence for an effect of cortisone on resistance to intracutaneous injection which is independent of hyaluronidase inhibition.

Baker has reviewed the effects of adrenal steroids on tissue histology (170) and hair growth (171). Ingle & Baker (172) have demonstrated a permissive action of adrenal extract on the inhibitory effect of estrogens on hair growth in the rat.

Circulation and central nervous system.—The adrenalectomized dog shows a decreased blood pressure response to norepinephrine (173). Adrenal

extract, but not DCA, restores this response to normal but not above. Kurland & Freedberg (174), on the other hand, found a striking potentiation of the pressor response to norepinephrine in human beings treated with ACTH or cortisone. Both cortisone and ACTH appear to raise hepatic blood flow and splanchnic oxygen consumption in man (175).

Schieve *et al.* (176) describe a decrease in cerebral blood flow without any change in oxygen or glucose utilization in patients receiving ACTH, while Bergen *et al.* (177) report a decrease in brain blood flow and oxygen consumption in adrenalectomized rats.

Woodbury (178, 179) and Fingl *et al.* (180) have reported on the effects of adrenal steroids alone and in combination with anticonvulsant agents on the electroshock threshold in rats. DCA and Compound S increased electroshock threshold (178) and had an additive effect when given with anticonvulsant agents (179). Compounds F, E, and A (in order of effectiveness) decreased electroshock thresholds and the hypersensitivity to electroshock so induced could be prevented to varying degrees by DCA (178) and anticonvulsant agents (180). Torda & Wolff (181) claim that ACTH decreases the sensitivity of rats to the convulsion-inducing effects of pentamethylene tetrazole even in the absence of the adrenal cortex.

Work performance.—Ingle and collaborators have presented new data on factors in muscle work performance by adrenalectomized animals. Continuous intravenous infusion of glucose improved work performance, but this improvement correlated more with the total fluid load than with the dose of glucose (182). Cortisone administered either subcutaneously or by continuous intravenous infusion improved work performance, but was less effective than hydrocortisone similarly administered. Neither was as effective as adrenal cortex extract administered by continuous intravenous infusion (183 to 185). These experiments suggest that full adrenal activity is not accounted for by the actions of either of the above steroids and draw attention again to other factors, such as those in the amorphous fraction.

The Control of Pituitary Adrenal Function and The Response to Stress

Long (186) has summarized his views concerning the mechanisms of the regulation of ACTH secretion, emphasizing that there must be several mechanisms at play. One, concerned with the rapid release of ACTH, appears to be mediated by the sympathetic nervous system and another involves a self-regulatory system presumably related to the blood levels of ACTH and adrenal cortical steroids. In support of the first mechanisms, Farrell & McCann (187) claim to have detected an increase in blood ACTH levels within 1 min. of an intravenous injection of 1.25 to 10.0 μg. of epinephrine into rats, and Gemzell (188) records increased body fluid and a decreased pituitary content of ACTH 48 hr. after injection of epinephrine in oil in normal rats. Estrogen increases plasma ACTH levels with no change in pituitary ACTH levels. Nelson *et al.* (189), on the other hand, found no

detectable rise in blood 17-hydroxycorticosteroids in normal men during or following a 4-hr. intravenous infusion of 1 to 3 mg. of epinephrine. ACTH and electroshock therapy in man (190) and acute whole-body ionizing radiation in dog (191) are, however, followed by rises in blood 17-hydroxycorticosteroids, but, surprisingly, normal levels were found in several patients with acute or chronic diseases except terminally. In the ill subjects with normal levels, it would appear that adrenal steroid production and removal are in balance. High levels of corticosteroids during stress are difficult to reconcile with the self-regulatory mechanisms by hormone utilization unless, as originally suggested by Tepperman *et al.* (192) and by Long (186), another factor, such as some metabolic consequence of the stress itself, is also concerned in sustaining the high secretory response. In this regard, the finding of Shepherd *et al.* (193) that cold exposure caused depletion of adrenal cholesterol, in both fed and fasted diabetic rats but not in fed normal rats, is interpreted by them as evidence for a metabolic factor in the control of pituitary-adrenal secretion during cold stress. Fortier *et al.* (194) question the self-regulatory mechanism suggested by Sayers since they were unable to prevent with cortisone adrenal ascorbic acid depletion in response to various types of stress. The same investigator (195) found that epinephrine, cold, and histamine caused eosinopenia in hypophysectomized rats with homotransplanted pituitaries in the anterior chamber of the eye, while immobilization and sound were effectual in controls but not in the grafted animals. This may be taken as further evidence for a neurohumoral mechanism of ACTH release. Sawyer (196) reports the blocking of epinephrine and formalin eosinopenia by an adrenergic blocking agent SKF-501[1]. The small, but significant depletions in adrenal ascorbic acid found by Vogt after insulin hypoglycemia (197) and emotional stimuli (198) in unilaterally adrenalectomized, demedullated rats is presented as evidence that epinephrine secretion is not solely responsible for the immediate pituitary adrenal response to these stimuli. Pickford & Vogt (199) were unable to detect any increase in corticoids over the low basal values in the adrenal vein blood of hypophysectomized dogs not receiving substitution therapy after epinephrine infusion, but were uncertain as to whether or not some increased secretion might occur in ACTH-maintained dogs given epinephrine. Tang & Patton (200) and Barrnett & Greep (201) found a normal adrenal response to cold exposure in the stalk sectioned guinea pig and rat respectively. In the first case, no significant evidences of panhypopituitarism developed, but, in the latter, pituitary and target gland atrophy were noted, even though both the adrenal and thyroid showed a response to cold exposure. Finerty & Hess (202) state that thyroidectomized rats exhibit a greater depletion of adrenal ascorbic acid after a scald than do control animals. The claim is made (Rose, 203) that the intrathecal administration of epinephrine stimulates the pituitary-adrenal axis by a direct action on the hypothalamus or pituitary and not by a peripheral mechanism.

Regardless of the complexities of the regulation of pituitary-adrenal

secretion by stressful stimuli, it is generally agreed that under other circumstances the rate of ACTH secretion is sensitive to levels of circulating corticoids. This is borne out by the recent demonstration by Gemzell *et al.* (32) and Sydnor & Sayers (33) of increased blood levels of ACTH after adrenalectomy in rats. The former investigators also noted an initial decrease in ACTH content of the pituitary after adrenalectomy. Epinephrine partly prevented the rise in plasma ACTH but accentuated the fall in pituitary ACTH, findings interpreted by Gemzell (188) to indicate an inhibition of ACTH formation but a stimulation of ACTH secretion.

The effectiveness of cortisone in the treatment of congenital adrenal hyperplasia is likewise consistent with the concept that corticoids suppress ACTH secretion [Wilkins *et al.* (204, 205)]. However, the observation by these workers that ACTH did not increase 17-ketosteroid excretion in these patients while receiving cortisone, whereas the stress of infection or withdrawal of cortisone therapy did, necessitates caution in interpreting these results.

The question of the functional capacities of the pituitary-adrenal system in the foetus and newborn continues to excite speculation. The adrenal glands of chick embryos show an increasing content of ascorbic acid during development (206). "Hypophysectomy" by decapitation prevents this change, suggesting that it is dependent on foetal pituitary secretion. Similarly, Kitchell & Wells (207) find that decapitation of the rat embryo retards growth and development of the foetal adrenal and this deficiency can be overcome by ACTH treatment. Compensatory hypertrophy of the remaining adrenal occurs after unilateral adrenalectomy in the 20-day rat foetus and can be prevented by cortisone (208). No detectable amounts of ACTH could be found by Jailer (209) in rat pituitaries until the animals reached 18 days of age. Presumably the pituitary does not store ACTH until this age and does not increase secretion in response to a single stimulus, but is apparently capable of increasing secretion in response to a sustained stress.

Engel (210, 211) has reported on additional studies on the interdependent roles of the adrenal cortex and stress in metabolism. With regard to nitrogen metabolism, the "catabolic" response to stressful stimuli was found to be much more rapid than that to either ACTH or adrenal steroids, provided adrenal hormone was present when the stimuli were introduced. In both cases, the metabolic response could be modified by simultaneous glucose or amino acid treatment. Adrenal hormone overdosage appeared to sensitize the organism to respond with changes in nitrogen metabolism to stimuli which otherwise did not have detectable effects on nitrogen metabolism. Similarly, a much more marked impairment in glucose tolerance could be demonstrated in ill subjects, following a single oral dose of cortisone, than in normal healthy subjects even when the latter received twice as much cortisone (212). The electrolyte excretion of adrenalectomized rats, maintained on adrenal cortical extract and subjected to leg fractures was found by Ingle *et al.* (213) to be quite comparable to that seen in intact rats simi-

larly traumatized. Eliel *et al.* (214) made a careful study of two patients undergoing surgery and maintained on constant caloric and protein, but variable potassium and phosphorus intake. They observed loss of protoplasm as indicated by negative nitrogen, potassium, and phosphorus balances, intracellular depletion of potassium and phosphorus, metabolic alkalosis and hypochloremia, eosinopenia and increased urinary excretion of uric acid, creatine, formaldehydogenic steroids, and 17-ketosteroids. These changes could not be prevented by increased potassium or phosphorus intake and could not be reproduced in their entirety by potassium deprivation alone. However, they are strikingly similar to the changes seen in patients with hyperadrenocorticism. In this regard, Nelson *et al.* (190) found considerably increased blood levels of 17-hydroxycorticosteroids in a patient with metabolic alkalosis. While all these data are consistent with the view that adrenal hypersecretion occurs following injury and the metabolic changes are manifestations of the resulting hyperadrenocorticism, examination of other data of Pearson & Eliel (81) clearly demonstrates that patients who are receiving large doses of ACTH or cortisone, but are in a stable state metabolically, may exhibit the same marked alterations noted above in response to the stress of an infection without any striking changes in corticosteroid excretion (215). It is apparent that considerable more investigation is necessary before it is possible to accept without question the simple notion that the metabolic alterations after injury are direct consequences of hypersecretion of adrenal steroid per se even though the latter indisputably occurs. Available data certainly suggest that some of these metabolic reactions are intrinsic features of the response to stress itself, and that adrenal hormone in adequate amounts is necessary only to sustain these reactions. In some manner, as yet undisclosed, the presence of a plethora of adrenal hormone appears to potentiate the metabolic response to stress (210, 211, 212). Ingle has presented a stimulating discussion of his views on this subject (216).

Stressful stimuli excited a lymphocytosis in adrenalectomized mice compared to the lymphopenia seen in intact animals (217), and larger amounts of cortisone were necessary to maintain normal lymphocyte levels in stressed than in unstressed adrenalectomized mice (218). The latter result is consistent with the interpretation that adrenal hormone is "used up" during stress. Hyperthermia causes eosinopenia, lymphopenia, and neutrophilia in intact rats. The entire response is abolished by combined hypophysectomy and adrenalectomy, but neutrophilia persists after adrenalectomy alone (219). Eosinopenia, but not lymphopenia, is reported in sodium chloride-deficient rats (220). Studies on the role of the adrenal cortex in blood formation and bone marrow cytology have been made by Gordon *et al.* (221) and Hayes & Baker (222), and in lymphoid tissue histology by Baker, Ingle & Li (223). Spiers (224) discusses the technique of eosinophil counts. The possibility that small intestine mucosa is the source of blood eosinophils is suggested by Godlowski (225).

Small doses of cortisone protect adrenalectomized mice from thermal burns, but larger doses decrease resistance to the burn (226). Neither ACTH, cortisone, or cortisone and ascorbic acid protected guinea pigs against the lethal effects of diphtheria or shiga toxin or meningococci suspended in mucin (227); but ACTH and cortisone did increase the resistance of mice to semilethal doses of arsenite, oxophenarsine and chlorarsen, but not to a number of other organic compounds (228). Adequate doses of ACTH or cortisone inhibited the pyrogen response to shiga endotoxin in rabbits, but less intensive hormone treatment not only failed to prevent fever, but the rabbits seemed to exhibit an aggravated febrile and systemic response to the toxins (229). Sellers *et al.* (230, 231) report that when rats are completely clipped and then exposed to a cold environment, they succumb rapidly. If previously acclimated by living in the cold for two months before clipping, both normal, adrenalectomized, and thyroidectomized animals show considerable resistance to cold exposure after clipping. Pretreatment of nonclipped, nonacclimated rats with a combination of cortisone and thyroxine increased survival but not as effectively as natural acclimatization. Houssay (232) has reviewed the effects on the adrenal cortex of hypoxia and histamine intoxication.

Active interest in the relation of ascorbic acid to stress and the function of the adrenal cortex continues. The subject has been reviewed by Pirani (233). Attempting to explain their earlier observations that ascorbic acid prevents adrenal hypertrophy after cold exposure, Dugal & Therien (234) and DesMarais & Leblanc (235) now find that vitamin C potentiates the effects of ACTH on adrenal weight and size and cholesterol in the hypophysectomized rat. Skelton & Fortier (236), on the other hand, were unable to detect any effect of ascorbic acid administration on adrenal cholesterol, but found the fall in adrenal ascorbic acid to be partly inhibited after ACTH treatment of hypophysectomized rats given ascorbic acid. Bacchus *et al.* describe increased liver glycogen deposition in adrenalectomized mice (237) and prolonged lymphopenia and eosinopenia in adrenalectomized rats (238) treated with cortisone and ascorbic acid, compared to animals treated with either agent alone. They suggest that a metabolic synergism exists between cortisone and vitamin C, and that this might be responsible for the nonactivation of the pituitary-adrenal axis implicit in Dugal & Therien's original experiment on cold exposure. The observation of Booker *et al.* (239) that combined treatment of adrenalectomized mice with ascorbic acid and either cortisone or adrenal extract confers greater protection against cold exposure than steroid treatment alone is consistent with this interpretation. Banerjee & Deb (240) report a decrease, Clayton & Prunty (241) an increase in urinary excretion of 17-ketosteroids in scorbutic guinea pigs. Bacchus *et al.* (238) refer to unpublished observations that ascorbic acid decreases the urinary excretion of 17-ketosteroids in cortisone-treated adrenalectomized rats. Clayton & Prunty were unable to demonstrate any modification in the scorbutic process by treatment with either ACTH or

cortisone. These results are at variance with those of Eisenstein & Shank (242) and Herrick *et al.* (243) who confirmed the findings of earlier investigators that ACTH or cortisone treatment increased the survival and delayed and modified the symptoms and tissue changes in guinea pigs on a scorbutic diet. Plasma ascorbic acid levels fall in adrenalectomized and hypophysectomized rats, and stress produces the same pattern in plasma ascorbic acid levels in the latter animals as in normals (244).

Anterior Pituitary

Chemistry and properties of pituitary hormones.—Continuing progress in the purification of pituitary hormones makes necessary considerable caution in interpreting studies on the metabolic and biologic effects of pituitary hormones previously considered chemically or biologically pure. It is becoming increasingly probable that there is more than one hormone with direct metabolic activity secreted by the anterior pituitary so that effects which have been previously attributed to growth hormone may not be so interpreted with complete assurance. In the following discussion, the term growth hormone will be used with this qualification in mind.

Raben & Westermeyer (245) have described a modified procedure for isolation and purification of growth hormone as a by-product in the isolation of ACTH, using extraction in glacial acetic acid at 70°C. and removal of ACTH by adsorption on oxycellulose. This preparation was found to be free of ACTH, thyrotropin, gonadotropin, and posterior lobe principles and contained only traces of luteotropin, adipokinin, and intermedin (246). Most significantly, this hormone proved effective for the first time on record in inducing nitrogen and phosphorus retention in man—in this case, a 26-year old female with panhypopituitarism. Furthermore, the hormone was free of diabetogenic activity when tested on dogs demonstrably sensitive to the diabetogenic activity of other so-called growth hormone preparations (246, 247)[5]. If confirmed, these observations represent the most significant development of the year in the field of pituitary hormone chemistry and physiology. The claim that growth and diabetogenic activities are separate is at variance with the results of Reid (248) who was unable to modify the ratio of growth promoting to diabetogenic activity of growth hormone preparations by a variety of chemical procedures. Biological activity appeared to depend on the integrity of the free ϵ-amino groups and not on the free α-amino groups of the growth hormone molecule (248, 249). From studies on the hydrolysis of growth hormone with crystalline chymotrypsin and

[5] Reid (316) has failed to confirm in its entirety Raben & Westermeyer's claim (247) that growth hormone prepared by their technique is free of diabetogenic activity. When injected at an alkaline pH, Reid found the diabetogenic activity of this growth hormone to be quite high in relation to growth promoting activity. When prepared at an acidic pH, as was done by Raben & Westermeyer, no diabetogenic activity was observed following treatment with the same preparation of growth hormone.

carboxypeptidase, Condliffe & Li (250) conclude that COOH terminal end groups are not essential for biological potency of growth hormone.

Nitrogen metabolism and growth.—Walker *et al.* (251) have succeeded in hypophysectomizing six-day-old rats. Such rats invariably died prior to the eightieth day of life, presumably from neural damage cause by dwarfing of the crania. If treated with growth hormone, normal cranial growth and survival resulted, but normal renal and skeletal differentiation did not occur. The effects of pituitary factors and thyroxin and skeletal morphogenesis in the rat have been reviewed by Asling, Simpson & Evans (252). Nielsen (253) finds that growth hormone and thyroxine produce normal bone growth in mice with hereditary pituitary dwarfism, administration of both hormones together being more effective than either alone, a result comparable to that of Asling *et al.* (252) in hypophysectomized rats. Hypervitaminosis A accelerates bone growth sequences in hypophysectomized rats, indicating that this effect of vitamin A is not mediated by the anterior pituitary (254). Hypophysectomy decreases wool growth in sheep, a response which is not explained by deficiency of either growth hormone or thyrotropin (255). Wang *et al.* (256) report increased hatchability, body weight, and elevated blood sugars in chick embryos treated with 10 μg. of growth hormone on the thirteenth day. Ershoff (257) was unable to promote an increase in weight by growth hormone treatment, of immature rats exposed to cold while Selye (258, 259), on the other hand, effectively prevented with growth hormone the weight loss resulting from the stress of turpentine injection and ionizing radiation in mature rats. Similarly, Smith *et al.* (260) were able to induce greater weight increments in C3H mice bearing a transplantable mammary adenocarcinoma by treatment with growth hormone, both tumor and host participating in the increased growth.

A number of publications have appeared which have bearing on the mechanism and site of action of growth hormone in protein metabolism. Using the rate of accumulation of urea in the blood of nephrectomized rats as an index of protein metabolism, Russell (261) found no effect of purified growth hormone on the basal rate of urea formation, but significantly less urea was formed from injected amino acids in treated animals than in controls. These data were interpreted to indicate an effect of growth hormone on the retention of amino acids in the tissues rather than on the catabolism of amino acids. On the other hand, Maassen (262) noted decreased urea and ammonia nitrogen production by liver slices from growth-hormone-treated rats. Bartlett, Gaebler & Mathies have continued their productive studies on the mechanisms of nitrogen storage and growth induced by growth hormone in normal and hypophysectomized rats (263 to 270). Muscle transaminase activity of rapidly growing rats was found to be lower than that in adult normal and immature hypophysectomized rats. Low doses of growth hormone produced a significant decrease in transaminase activity in the latter preparation. Concentrations of total amino

acid carboxyl nitrogen were lower in skeletal muscle during induced growth in hypophysectomized rats and in rapidly growing, normal rats, compared to normal or untreated hypophysectomized rats. No *in vitro* effect of growth hormone on transaminase activity could be detected (263). A fall in liver weight and an increase in hepatic transaminase were noted in pair-fed hypophysectomized rats treated with growth hormone and in normal rats on a restricted food intake (264). These findings were interpreted as being consistent with the inverse relationship which has been postulated to exist between transamination and protein synthesis. Under the conditions of these experiments, protein synthesis was presumed to be occurring in muscle, while liver protein was undergoing catabolism, since food intake was inadequate to support the enhanced protein synthesis in muscle. The authors suggest that growth hormone might initiate a mechanism for conservation of glutamic acid and the subsequent concentration of amino acids, promoting nitrogen storage and intracellular synthesis of protein. Cathepsin activity of kidney, liver, and spleen of hypophysectomized rats were lower than normal, and were only partially restored by large doses of growth hormone. Thyroxin, on the other hand, increased the cathepsin activity of tissues of both normal and hypophysectomized rats, suggesting that the low values in the latter should be more properly ascribed to thyrotropin deficiency (265, 266). Dehydropeptidase I activity, which has been correlated with catabolic processes of protein metabolism, was observed to increase progressively in liver and kidney from lowest values in hypophysectomized rats to intermediate levels in growth-hormone-treated, hypophysectomized immature rats; to significantly higher values in rapidly growing immature rats; and to the highest value in normal adult rats (267). The slight effect of growth hormone on dehydropeptidase I activity was interpreted as consistent with the view that this hormone has little influence on protein catabolism. Further support for the concept of these investigators, that growth hormone regulates the intracellular synthesis of protein by promoting amino acid storage (263), was derived by actual measurements of the size of the nitrogen pool in growth-hormone-treated dogs (268, 269). Using the technique of Sprinson & Rittenberg (271), the size of the nitrogen pool was found to increase 44 per cent during induced growth with growth hormone, while amino acid catabolism decreased 42 to 67 per cent and the rate of protein synthesis increased 8 to 18.5 per cent. Small changes in total plasma protein concentration occurred, but a marked increase in specific activity of the major plasma proteins was found (270). This was most striking in the globulin-rich, protein fractions which were rapidly synthesized and utilized, presumably by incorporation into tissue protein.

Milman, DeMoor & Lukens (272) have reported on painstaking investigations which help clarify the interrelationships between insulin and growth hormone in growth. In depancreatized cats on a constant food intake and insulin dosage, nitrogen storage varied directly with the dose of growth hormone, but not vice versa; i.e., on constant growth hormone dosage, there

was no relation between the dose of insulin and the amount of nitrogen retained. In the absence of insulin (hypophysectomized-depancreatized cat), growth hormone had no nitrogen-retaining effect. The authors conclude that insulin is essential for the nitrogen-retaining effect of growth hormone. Wijnans & De Jongh (273) support this conclusion by demonstrating that growth hormone does not lower the blood amino acid content of alloxan-diabetic, eviscerated rats unless insulin is present.

Despite significant increases in weight and cross section of rat quadriceps muscle after growth hormone treatment, Bigland & Jehring (274) found that muscle performance per gram of muscle was less than normal. Scow (275) reports that growth hormone has little effect on formation of muscle tissue in the absence of the thyroid, but increases muscle collagen.

Carbohydrate and fat metabolism and diabetes.—Illingworth & Russell (276) have analyzed the acute *in vivo* effects of growth hormone on carbohydrate storage in gastrocnemius muscle, heart, diaphragm, and liver of normal, hypophysectomized, adrenalectomized, and alloxan-diabetic rats, and compared these to the effects of insulin. Growth hormone exerted its greatest effects on cardiac glycogen levels, while insulin influenced diaphragm glycogen to the greatest degree. A permissive action of adrenal cortical hormone was indicated in the growth hormone response, confirming older findings with crude anterior pituitary extract. The authors suggest that the glycogen storage noted following growth hormone treatment is a consequence of diminished carbohydrate oxidation or fat formation, the rate of carbohydrate catabolism being inhibited to a greater degree than glycogen formation. It is unlikely that any of the above effects of growth hormone are either mediated by or dependent on insulin, in contrast to the nitrogen-retaining actions of growth hormone (272).

Other studies give increasing support to the concept that there may be more than one factor in crude anterior pituitary extract concerned with carbohydrate metabolism (277). Thus, there appears to be one factor, probably responsible for the effects noted by Illingworth & Russell (276), which causes an increase in glucose utilization and glycogen accumulation in rat diaphragm *in vitro*, both soon after injection into the rat, as well as on incubation with diaphragm *in vitro* (278). This factor apparently is the same as that which has been known to induce hypoglycemia in fasted animals. There is also a factor which lowers the respiratory quotient that is being investigated by Recant (279, 280). The material is closely associated with, but not identical with, growth hormone since loss of R. Q. activity may be produced without loss of growth-promoting activity. Its *in vitro* addition to diaphragms from fasted rats prevents the rise in R. Q. ordinarily noted in the presence of glucose and hexosediphosphate, but not when 3-phosphoglyceric acid, pyruvate, or acetate serve as substrate. The R. Q. depressing activity is not prevented by insulin. The data suggest that this factor causes a block somewhere between hexosediphosphate and pyruvate. A material with comparable activity has been found in the serum

of fasting normal rats, normal humans and those with diabetes mellitus, but not in serum from hypophysectomized rats or fed humans (280). Another action of pituitary extract *in vitro* is in the direction of causing decreased glucose uptake and an inhibition of the response of the diaphragm to insulin (277). It becomes apparent only several hours after injection of growth hormone, but can also be detected on incubation with diaphragm *in vitro*. It is probably identical with the factor found by Stadie (281) to inhibit the binding of insulin by muscle. Considerable more investigation is necessary before it will be possible to establish the precise interrelationships between growth-promoting activity of pituitary extracts and the various other effects on carbohydrate and fat metabolism and in diabetogenic activity.

Using the ADHA[1] rat as a test object, Bornstein, Reid & Young (282) present evidence that blood from portal circulation of growth-hormone-treated, ADHA rats and intact cats has an hyperglycemic effect when injected intravenously into recipient ADHA rats. This was attributed to release of hyperglycemic factor from the pancreatic islets. Growth hormone itself had no effect and femoral vein blood caused a slight fall in blood sugar, possibly owing to the presence of insulin. Kurtz *et al.* (283) found that purified growth hormone still induced hypoglycemia in acutely depancreatized dogs, indicating that the pancreas is not necessary for this response, but they could not rule out the possibility that insulin still persisting in the circulation was necessary for the hypoglycemic response to growth hormone.

Young (284, 285) has reviewed his concepts concerning the relation of the anterior pituitary to diabetes mellitus. Support for his view, that growth hormone becomes diabetogenic when the organism cannot respond to it fully by growth, appears in the report of Engel *et al.*, who find that rats, force-fed a high carbohydrate diet, exhibit hyperglycemia and glucosuria when the growth response to growth hormone is inhibited by subdiabetogenic doses of ACTH (286) or thyroid (287). Glycosuria always disappeared on stopping either hormone. Reid (288) has likewise noted potentiation of the diabetogenic effect of growth hormone by ACTH in cats. DeBodo *et al.* (289) report growth hormone to be diabetogenic in the hypophysectomized dog, and Campbell *et al.* (290) confirm the diabetogenic effect of purified growth hormone in the intact dog. Russell (291) found that considerably larger amounts of growth hormone (30 to 50 mg./kg.) were necessary to enhance glycosuria in alloxan-diabetic rats than in the intact dog or cat (1 to 3 mg./kg.), or for that matter, in the ACTH-treated, force-fed rat (10 to 30 mg./kg.) (286). Growth hormone increased the glycosuria of depancreatized cats on a constant dose of insulin and as well as that of Houssay cats (272). In the latter case there was no increase in nitrogen excretion, in contrast to the response of the same cats to ACTH. Reid (292, 293) has described a method for assaying pituitary preparations for their diabetogenic activity using intact cats. Partial success is reported in the treatment with growth hormone of a case of hyperinsulinism caused by islet cell adenoma (294).

According to Brady, Lukens & Gurin (295), the conversion of C^{14} acetate

to fatty acids in cat liver slices is stimulated by hypophysectomy or insulin treatment and inhibited by pancreatectomy or growth hormone treatment, but is normal in the absence of both pituitary and pancreas. Growth hormone had no inhibitory effect on lipogenesis when added directly to rat liver slices, but it inhibited the stimulating effect of insulin.

Campbell & Davidson (296) report that an anterior pituitary preparation administered to fasting rats increases the oxygen uptake and acetoacetate production of liver slices, an effect which could not be reproduced fully by the action of purified growth hormone or ACTH. The extract used had no effect *in vitro*. While the slices actively oxidized added octanoate with increased acetoacetate yield, the pituitary extract had no apparent effect on this reaction. According to Tepperman *et al.* (297, 298) ketone body production by surviving liver slices from hypophysectomized rats, is decreased compared to that by intact controls. The degree of depression of ketogenesis varies directly with the period of time elapsing after hypophysectomy. Injection of growth hormone restores the rate of ketogenesis in slices taken from rats less than 15 days after hypophysectomy, but not in those more than 30 days postoperative, unless the animals are pretreated with cortisone. Some adrenal activity thus appears necessary for ketogenesis. Certain, but not all, preparations of so-called growth hormone tested increased ketone body production from liver slices of large (300 to 400 gm.) fed rats. Somewhat similar findings are reported by Levin (299, 300) with respect to mobilization of liver fat during fasting and stress. A pituitary factor, which cannot be identified as either ACTH or growth hormone per se, triggers fat mobilization. Adrenal cortical hormone must be present for the reaction to occur, but the latter is itself not responsible for fat mobilization. The fat mobilizing and ketogenic factor(s) apparently travels closely with both ACTH and growth hormone, since both the latter may induce fatty livers and ketosis in cortisone-maintained, adrenalectomized animals (299, 122). These results again emphasize the need for further attempts at the chemical separation of pituitary factors.

Miscellaneous.—The ability of the totally hypophysectomized dog to handle a water load is impaired, but this animal has been found to be quite capable of withstanding sodium restriction or potassium loads despite generalized atrophy of all three zones of the adrenal cortex (301, 302). Growth hormone improves the totally hypophysectomized dog's ability to handle a water load and, indeed, increases water exchange to the level expected in diabetes insipidus (303). Reinhardt & Li (304) were unable to confirm the latter result in hypophysectomized rats. Leaf *et al.* (305) failed to reinduce polyuria and polydipsia in a patient with diabetes insipidus alleviated by spontaneous anterior pituitary insufficiency, by treatment with the Raben-Westermeyer growth hormone (245). This preparation was effective in inducing positive nitrogen balance in man. Hofmann (306) reports that adrenalectomy further reduces the impaired water excretion of hypophysectomized rats. Purified growth hormone (Li) caused a reduction

in the urinary sodium and potassium excretion of normal female and partially depancreatized male rats (307, 308). Certain but not all preparations of growth hormone increase *p*-aminohippurate and inulin clearances in normal and hypophysectomized dogs (309). The Raben-Westermeyer preparation proved ineffectual in this regard in a hypopituitary patient (305). The uptake of Ca^{45} by the tibias of hypophysectomized rats is increased by growth hormone treatment (310). The decreased renal and tibial alkaline phosphatase activity of hypophysectomized rats likewise may be restored by treatment with growth hormone (311). An influence of the pituitary on copper metabolism has been reported (312). Cobalt is reported to prevent the anemia of hypophysectomy (313).

Lemonde *et al.* (166) have made the important observation that enhanced susceptibility of cortisone-treated rats to infection with tuberculosis can be overcome by concomitant treatment with growth hormone.

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REPRODUCTION[1,2]

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In 1910, the late Dr. F. H. A. Marshall published the first edition of his *Physiology of Reproduction*. It represented the first attempt to assemble in the English language the knowledge that was available about the subject of reproduction. A second edition appeared in 1922, but unfortunately missed the very rapid expansion of the subject, especially on the endocrinological side, which took place during the 1920's. A third edition of Marshall's classic, of which one volume has now been published under the editorship of Parkes, again brings the subject up to date, and in the same encyclopaedic form first attempted by Marshall himself.

The volume that has appeared (Vol. II) corresponds to the second half of the single volumes of the first and second editions (1). Its chapters deal with the history of the fertilized ovum, cleavage and implantation, placentation, foetal and maternal physiology, parturition, lactation and fertility, and show up, very clearly, the areas in which most progress in knowledge has been made in the past 30 years.

Since 1922, we have been provided with detailed knowledge about the chemistry and cytological nature of the ova of different species. Developments in microscopy and in methods of tissue culture have made possible the direct study of cleavage in many mammalian species. Another achievement of the past 30 years is an understanding of the transport of sperm and ova, and of the factors concerned in the spacing of blastocysts, matters which, in the second edition of Marshall's book, could be dealt with in very few words, in spite of the fact that artificial insemination of farm animals was already being practised. On the other hand, the precise roles of blastocyst and endometrium in the process of implantation are as uncertain today as they were 30 years ago, even though the actual facts of implantation may be very much better understood, not only in nonprimate mammals but also in monkeys and man. We owe this advance mainly to the fact that it has become possible to obtain for study material that can be timed in relation to the ovarian and uterine cycles.

The 1910 chapter on "Foetal Nutrition and the Physiology of the Placenta" was reprinted almost unchanged in 1922, Marshall noting at the time that little new on this subject had appeared in the preceding decade. Information about the macro- and microscopic structure of the placenta is now

[1] The survey of the literature pertaining to this review was completed in June, 1952.

[2] The following abbreviations are used in this chapter: DCA (desoxycorticosterone acetate); PAS (periodic acid-Schiff); LH (luteinizing hormone); CG (chorionic gonadotrophia); FSH (follicle stimulating hormone); PMS (pregnant mare serum); ACTH (adrenocorticotrophin).

so considerable that it fills an entire chapter nearly 200 pages long. The physiology of the placenta also now requires a chapter of its own, but in spite of this its authors begin with the remark that the subject is in its infancy. The second edition disposed of the topic of the experimental production of deciduomata in a single paragraph, whereas several pages are now required to review this question. The new chapter on placental physiology is also concerned with a detailed analysis of the growth changes which occur in the pregnant uterus and with the way the nutrition of the embryo is mediated by the maternal and foetal placentae. It deals at length, too, with the placenta as an endocrine gland, an idea which was little more than speculation when the second edition was published.

An entirely new chapter on foetal respiration and circulation is based on work published in the 30's and 40's, much of it associated with the name of the late Sir Joseph Barcroft. The succeeding chapter provides an excellent description of the normal physiological changes in the maternal organism during pregnancy.

The chapter on parturition adds little that is either new or that seems likely to provide us with an understanding of the factors controlling the processes of birth. By contrast, lactation is yet another subject which is shown to have benefited greatly from the application of modern biochemical and physiological methods of study. It is clear that we now know a great deal about the chemical processes within the cells that lead to the formation of milk, even though we remain uncertain about the factors that control the onset of lactation.

The chapter on fertility, in the new edition as in its predecessor, begins by considering various generalizations about population growth and ends with a statement of the world's human population problem. It provides a very useful indication of the improvement that there has been in the scientific breeding of animals over the past 30 years. During this period our knowledge of genetics has also grown vastly, a fact which expresses itself in the much more detailed study of the mechanism of sex-determination in *Drosophila*, Amphibia, fish, and mammals that is now possible. Unfortunately, we still appear to be as far as ever from a knowledge of the primary sex-ratio at fertilization in man (see p. 447). In spite of extensive studies on intersexuality, the new chapter also shows that the freemartin condition in cattle has still not been reproduced experimentally, and that the role of maternal and foetal sex hormones in the embryonic differentiation of the reproductive tract remains a controversial topic.

The last chapter of the new volume, like that of the second edition, deals with the life cycle and such matters as the onset of puberty and the climacteric changes which, in human beings, grade into senescence. While we are still far from understanding the factors which determine the onset or duration of reproductive life, it is all too ominously clear that, with the increase in the expectation of life, we are now becoming familiar with a variety of genetically-determined characteristics which are not manifest in youth and which provoke pathological changes in old age.

Reproduction in the Female

Oestrous cycle.—Information about the mammalian oestrous cycle continues to accumulate steadily, but no startling new facts have been reported during the past year. A general account of the cycle is provided by Bullough in a small book (2).

Reproductive processes in the ewe are dealt with in a comprehensive review (3). The time of onset of oestrus in the young animal depends not only on conditions of light but also on the rate of growth, and the sexual season lasts only a quarter to one-third as long as in adult sheep (4). In the adult the cycle can be shortened by distending the uterine lumen with a plastic bead. Denervation of the distended segment restores the normal oestrous cycle length (5). In the ferret the gonadal response to added light depends on the integrity of the ganglion cell layer of the retina (6). Field observations of the elephant, made by Perry (7) show that corpora lutea, formed either after ovulation or by luteiniziation of unruptured follicles, have a short life span when conception does not occur. When it does, a set of corpora lutea which is soon formed is replaced halfway through pregnancy by a set which persists to term. Detailed information about the length of the cycle in cows (8) has also been published this past year, and, as in the rat (9), it appears that cycle length varies much less in the same animal than between different animals. Cycles which follow sterile mating are about five days longer than the normal cycle. In rats, the duration of oestrus is much more constant than the duration of dioestrus (9), and it was confirmed that vaginal cycles continue after spaying (10). The duration of the cycle after spaying remains unchanged, but the "oestrous" phase is shorter. The administration of a constant amount of oestrogen combined with either androgen or DAC[2] to spayed rats results in five day-cycles of vaginal cornification (11). Adrenalectomy increases the sensitivity of the vagina to oestrogen so that constant oestrus takes the place of the "artificial" cycles. The histological characteristics of the reproductive tract of spayed guinea pigs (12) and of spayed women (13) also suggest that oestrogen is still being produced after removal of the ovaries.

Detailed information about the breeding of dogs under "colony conditions" is presented by Rowlands (14). The oestrous cycle lasts 7.7 months. The conception rate was 82 per cent, and single mating was significantly less fertile than multiple mating. The sex ratio of live births was 117:100 (383 male and 328 female puppies). The still birth sex ratio was 100:100, but more male pups died, and at weaning the sex ratio was 102:100.

Studies have also been made of the reproductive physiology of the Alaskan fur seal, which ovulates a single ovum within a week after parturition. Ovulation occurs from alternate ovaries in successive years. While all the seals ovulate, losses of ova and embryos may be as high as 24 per cent. The blastocyst remains unattached for 3½ to 4 months (15).

Modifications of reproductive behaviour in animals kept in zoological gardens have been described by Hediger (16, 17, 18). Captive animals may become either hyper- or hyposexual, and Hediger regards successful breeding

as an indication that satisfactory living conditions have been provided. He has succeeded in getting captive hares to breed successfully and has confirmed the fact, according to him, known to Herodotus, that oestrus occurs three to four days before parturition. If the does are then mated, superfoetation occurs, a second litter being born 38 days after the first.

In sows, postpartum oestrus occurs within three days of farrowing if the young pigs are removed (19). Puberty occurs at different ages in different strains of pigs (20 to 23). As a rule, fast growing strains reach puberty more slowly than slow-growing strains, but within a strain faster growing animals reach puberty earlier than slow-growing ones. Sperm are present in the epididymis of the pig two months or more before libido develops. A high protein diet retarded puberty but increased the number of ova released.

A number of other studies also emphasize the influence of diet on reproduction. Thus, incipient vitamin A deficiency reduces the ovulation rate and reduces the number of viable foetuses in rabbits (24). Reproduction in rats deficient in vitamin B_{12} becomes progressively worse, and after a time (e.g., the third litter) the young are usually born in such a debilitated condition that they will not survive even if foster-mothered (25). The intrauterine lesion responsible for this effect is unknown. Another study carried out on rats has shown that an unknown liver factor (not vitamin B_{12}) is also necessary if litters are to survive (26), and it is confirmed that in this species a restriction of calories may lead to anoestrus (27). This effect is not influenced by alterations in the protein content of the diet, so that a deficiency in amino acids cannot be held responsible for the anoestrus (28). Increasing the hours of illumination from 8 to 13 hr. daily compensates, so far as reproduction is concerned, for inadequacies of a stock diet used for rats (29). Sulphadiazine or sulphamezathine given to rats early in pregnancy decreases the size of the litter (30). Given to growing chicks, however, sulphamezathine and other similar pyrimidine compounds are again reported to stimulate testicular development (31).

Menstrual cycle.—During the past year little that is essentially new has been discovered about the menstrual cycle. A general review of its underlying hormonal mechanisms has appeared (32), and another review of menstrual physiology (33) emphasizes the need for more information about the influence of neural factors on menstrual function. That such factors do have an effect is indicated by the observation that prolonged bleeding may occur at times of emotional tension (34), and that sudden anxiety may precipitate uterine bleeding after amenorrhoea (35, 36). It is also stated that traumatic damage to the brain is more likely to disturb menstrual periodicity if the trauma is immediately followed by unconsciousness (37). Knaus discusses the part played by the ovary in determining the rhythm of menstruation (38).

Renewed interest in the histology of the endometrium of the rhesus monkey during the menstrual cycle is evinced by two papers based on the combined material from several large American collections (39, 40). These studies

failed to substantiate the belief that the greater part of the endometrium sloughs off at menstruation, and that the mucosa is restored by proliferation of the basal layer. Only about one-third is actually involved, and very few mitoses can be found in the basal zone during the subsequent phase of repair. It was also found that the metachromatic ground substance, present in large amounts in the endometrium in mid-cycle, disappears by the time menstruation occurs. The paramount importance of changes in the hydration and concentration of ground substance in the mid-zones are also emphasized in this study. In the second investigation (40), attention has been paid to the number of mitoses in surface, superficial, and basal glands of normal monkey endometria. Most mitoses occur when large Graafian follicles are present in the ovary, but cellular division continues into the luteal phase, when the site of mitotic activity shifts from the superficial to the basal layers of the endometrium. Mitoses are almost absent during the late luteal and ischaemic phases, but reappear before the end of menstruation.

The structural changes which occur in the monkey uterus in response to prolonged treatment with oestrogen, progesterone, or both hormones together together have been described (41). There are widespread differences in the reactions of the stromal glands and arteries, but menstruation will occur when the supporting hormonal stimulus is withdrawn, whatever the nature of the preceding structural response. Earlier claims that there are cyclical changes in the histological appearances of the human endocervix have been denied (42).

Further information has been published about the "intracyclic bleeding" that can be induced by means of timed injections of progesterone or DCA. A condition that simulates epimenorrhoea can be produced (43, 44). The influence of prostigmin on the cycle remains a matter of controversy. It has been suggested that it induces bleeding in secondary amenorrhoea not only through some local action on the uterus but also as a consequence of a central effect on the diencephalon (45).

The use of oestrogens in clinical practice has tended to become standardized, and as a result there is little new to report about the comparative potency of oestrogens. The latent interval before bleeding for a series of compounds has been estimated in women, and this study confirms the view that esterification prolongs oestrogenic effects (46). Emulsions and suspensions of the hormones prolong them even more. An analysis of the relative potencies of 11 different oestrogens in spayed monkeys emphasizes the fact that the minimal dose needed to induce withdrawal bleeding is much less when successively smaller doses are given from a primarily effective level than when ineffective small doses are successively raised (47).

It is known that pronounced changes in water balance take place during the menstrual cycle, and that these are specially noticeable in species of subhuman Primates whose sexual skins swell. It has now been shown that the level of serum proteins (albumin fraction) fluctuates in phase with the cycle in baboons, even when allowances are made for concomitant changes in

haematocrit values (48). In women, oestrogenic stimulation also causes haemodilution, as indicated by changes in blood volume (49). It should, however, be noted that in cattle (and also in birds), oestrogen is said to have no effect on the albumin level but to increase β- and γ-globulin levels (50, 51). The concentration of plasma fibrinogen does not fluctuate as much in the male or the ovariectomized monkey as it does in the normal female (52). Cyclical fluctuations also occur in the amount of β-glucuronidase in the human vaginal epithelium, though there is no correlation between serum levels and the cycle (53).

Treatment with androgen has been shown to induce precocious uterine bleeding in prepubertal monkeys (54). Young female rhesus monkeys in a colony maintained in the Medical School of Yale University begin to menstruate at the age of two years and at a body weight of about $3\frac{1}{2}$ kg. One normal animal first menstruated at 17 months (55). These young rhesus monkeys become sexually mature much more rapidly than is usual in European surroundings.

Ellis (56) reports the very interesting finding that the age of puberty of African Negroes in Nigeria is later than is usual for English children. Wilson & Sutherland (57) have found that this is also true of the Sinhalese and they point out that in Ceylon, children in rural areas reach puberty much later than those brought up in the towns. These two sets of observations throw doubt on the widespread belief that puberty is reached earlier in the tropics than in more temperate zones.

Female reproductive tract.—Cyclic changes in the reproductive tract of the goat have been described (58), and the application of cytochemical methods to the study of endometrial and vaginal changes continues (59, 60). Further information has also become available about the extent to which the reproductive tracts of new born mammals may have been stimulated by sex hormones during intrauterine life. It is known, for example, that a foal's ovaries at term may be larger than its mother's, and that its endometrium may show signs of stimulation by oestrogen (61). At birth the ovaries of the seal also show the marks of stimulation by gonadotrophin (62), and the histological picture suggests that the foetal endometrium has been stimulated not only by oestrogen but also by progesterone.

The way in which different hormonal treatments affect the rate and extent of epithelial proliferation has been studied in the uterus of the immature rat (63, 64). Another study has shown that there are pronounced differences between different mammals in the specificity of the progestational response of the endometrium (65). Local application of progesterone, DCA, pregnenolone, ethisterone, or methyl testosterone, will induce progestational changes in the rabbit. In the cat only progesterone and DCA, and in the mouse progesterone alone, are effective. In the rat, oestrogen, and not progesterone, as in Primates, appears to control glycogen deposition in the epithelium of the uterus (66).

Neither oestrogen nor progesterone influences the rate or character of

postpartum endometrial regeneration in the guinea pig (67). The epithelium of the Fallopian tube in women becomes inactive postpartum, and by the twelfth day simulates the menopausal condition. Treatment with stilboestrol produced hyperplasia of the epithelium and also prevented the mild salpingitis which often occurs postpartum (68).

Aged dogs often develop an endometritis that seems to be associated with cystic ovaries. Dogs treated with oestrogen develop cystic endometrial hyperplasia only, but treatment with progesterone and oestrogen together produces a pyometritis which regresses when the treatment is stopped (69).

Endometriosis is a condition in women which seems to be of increasing importance in gynaecology, but its aetiology is still uncertain. So far it has not been produced experimentally in any species, and indeed has only very rarely been encountered in animals. This year its occurrence in monkeys has been reported twice (70, 71). Both instances are regarded as better explained on the basis of metaplastic changes in the coelomic epithelium than of the implantation of "regurgitated" endometrial fragments. In one of the two monkeys (71), the endometriosis was associated with ectopic supernumerary ovarian tissue embedded in the wall of the uterus.

Differences have been described in the contractile response of the human and ruminant uterus and cervix to various drugs, and further studies have been made of the influence of oestrogen and progesterone on oxytocics (72 to 75). Reynolds (76), who also discusses the relation between uterine contractility and cervical dilatation in normal and abnormal labour (77), provides a comprehensive review of factors which determine uterine growth and activity. The dominant role of the fundus in uterine movements appears to be due to a variety of morphological, physical, and chemical factors. The concentration of actomyosin in the fundus increases during pregnancy, and the contractility of the uterine muscle becomes almost as great as that of striated muscle.

The action of oestrone on the symphysis pubis, simultaneously resorbing and depositing bone, is not influenced by removal of the reproductive tract (78).

Ovary.—The difficulties of distinguishing normal and atretic follicles in the ovary have always been recognized by histologists, who have found it virtually impossible to establish reliable criteria that can be used to provide consistent estimates of the numbers of degenerating follicles. Argyrophilic granules, varying greatly in amount and disposition, have been reported in in the cytoplasm at all stages of development of the rat ovum. Large aggregates of the material are thought to suggest atresia which, it is felt, may be distinguishable in the ovum before changes in the granulosa cells are apparent (79). Cytochemical procedures have been used to detect atresia in the granulosa before karyorrhexis is apparent. The alkaline phosphatase increases and PAS[2]-positive material appears, especially in the cumulus cells. Neither ascorbic acid nor esterase are present in normal granulosa cells, but they are associated with the onset of atresia (80).

Further studies have been made to clarify species differences in the extent to which granulosal and thecal tissue contribute to the formation of the corpus luteum. Only one type of cell is present in the mature corpus luteum of the rat, but cells of thecal and granulosal origin can be differentiated in young corpora lutea (81). In the wild rat, as in the monkey, accessory corpora lutea resembling normal corpora lutea are formed by luteinization of unruptured follicles (82).

The development of interstitial tissue in the ovaries of young rats has been studied by histochemical procedures (83). A primary interstitial tissue which may be derived from granulosa cells, and which appears within a fortnight of birth, can be distinguished from secondary tissue which develops later from theca interna cells. The early development of the theca has been described in the guinea pig (84).

Hyperplasia of luteal cells of thecal origin in women is associated with a clinical syndrome of amenorrhoea, sterility, and hirsutism, but without raised 17-ketosteroids in the urine (85, 86). The condition is satisfactorily dealt with by "wedge resection" of the ovaries.

The usual battery of histochemical tests has also been applied to the sow's ovary on the assumption, which is still disputed, that positive reactions indicate the presence of steroid hormones and the sites of hormone production (87). Lipid droplets are found in the theca interna just before ovulation and for the next 15 days. Lutein cells derived from the granulosa show similar changes. Variations in the physical characteristics of the droplets suggest phases of activity. Even if these methods demonstrate steroids, the reactions are not sufficiently specific to identify individual hormones. Signs of activity in the theca interna cells of human ovaries have been detected by fluorescence microscopy, and are thought to indicate the presence of oestrogens (88). Autoradiography with P^{32} has also been used to demonstrate areas of activity within the ovary (89).

In recent years the study of the earliest stages of human embryology has been a lively field. This study has provided material for a detailed examination of the morphology and histochemistry of the human corpus luteum based on 48 ovaries removed at different times of the normal menstrual cycle, 28 specimens representing normal pregnancy (from the two-cell stage to 18 weeks) and 13 corpora lutea associated with abnormal ova (90). Soon after ovulation cells, called by the authors *k* cells, having hyperchromatic small nuclei and homogeneous eosinophilic cytoplasm containing ketonic lipid, get carried into the granulosa lutein layer either as a result of their own migration or by invagination of the theca cells. Until implantation has taken place, the histological appearance of the young corpus luteum of pregnancy does not differ from that found in the normal menstrual cycle. Subsequent luteal activity can be correlated with the activity of the trophoblast. If the ovum is deficient in trophoblast the corpus luteum soon regresses.

Ovarian tissue is more difficult to preserve by freezing than spermatozoa

or skin. Parkes & Smith (91, 92), however, successfully grafted into rats pieces of rat ovary that had been kept in a frozen state and then thawed.

The granulosa-cell and theca-cell tumours which develop in young adult mouse ovaries transplanted into the spleen are usually attributed to increased secretion of gonadotrophin. The ovaries of senile mice also respond in the same way (93). An increased incidence of ovarian tumours is not, however, observed in old women, who have large amounts of circulating gonadotrophin, and it is conceivable that the human senile ovary is refractory to gonadotrophin.

The response of the recipient to a graft of foreign tissue such as skin seems to depend wholly on the development of an immunity reaction. The factors involved in the response to grafts of endocrine tissues seem to be more involved. "Halsted's Law" implies that the physiological need of the recipient for the endocrine tissue affects the chances of its survival, and that the chances improve, the less the amount of the particular endocrine tissue possessed by the host. Spaying made no difference, however, to the chances of successful grafting of ovarian tissue into the anterior chamber of the eye of rabbits (94). Pieces of human ovary, and endometrium, can be grafted successfully into the chorioallantoic membrane of the chick, but seem to provoke an antibody reaction before the egg is hatched (95).

Oogenesis.—The reversal of the accepted belief that in most mammals oocytes are formed only during embryonic life, and possibly soon after birth, dates mainly from Edgar Allen's study of the mouse, published in 1923. The usual teaching since then has been that oogenesis continues into and during adult life, and also that cycles of mitotic activity in the germinal epithelium, preliminary to oogenesis, can be correlated with the phases of the oestrous cycle. The problem has been reviewed by Zuckerman (96), who discusses a wide series of experiments which failed to confirm these hypotheses (97 to 101). A prerequisite of such experiments is a reliable way of counting the number of oocytes in the ovary. Using a somewhat less elaborate technique, Block has estimated that the number of oocytes in the human ovary falls progressively with age (102, 103). When allowances are made for the influence of age, it appears (104) that the number of growing follicles in the human ovary is greater after ovulation; this observation excludes from consideration the primordial follicles which make up most of the oocyte population. Green & Zuckerman (105) could find no evidence of cyclic fluctuation in the total number of oocytes in the ovaries of the monkey during the menstrual cycle. A series of 250 ovaries obtained from postmenopausal women revealed nothing to suggest the neoformation of oocytes (106). Oehler (107) studied foetal and young human ovaries, and also found no indication that oogonia are derived from the germinal epithelium, or that there was a mass degeneration of primary follicles at the time of birth.

On the other hand, the application of tissue culture techniques suggests that the germinal epithelium of the foetal human ovary does play an important role in oogenesis (108, 109). Only those cultures which incorporated

germinal epithelium survived and proliferated for up to about 30 days of culture. New oocytes surrounded by one layer of follicular cells were formed. Cords of cells may develop from clumps of follicular cells after the ova that they originally surrounded have broken down, and new ova appear to form in these cords. Cultures of chick gonads will also grow and differentiate (110).

Multiovular follicles and multinuclear ova are common in the ovaries of newborn babies, but disappear during the first six months of life (111). Among the explanations that have been suggested for the occurrence of polyovular follicles are (*a*) division of polynuclear ova, (*b*) fusion of separate follicles, or (*c*) failure of developing granulosa cells to separate individual ova from each other. Dawson (112) has suggested a fourth possibility, that the first layer of investing granulosa cells may have oogenetic powers.

Desaive (113, 114, 115), working on the rabbit, has derived a series of mathematical laws of follicular growth, and believes that growth takes place in a series of discontinuous jumps from one stage to the next. There is, however, no evidence that such a process occurs in the ovary of the rat or monkey, where follicular growth seems to be a continuous process (116). The relationship between size of ova and size of follicle in the human is very similar to that found in other mammals (117).

Ovulation.—The process of ovulation has been actually observed in only a few species, notably the rabbit. Observations of the human ovary, made with the help of a culdoscope inserted into the pouch of Douglas, suggest that the ovarian ligament contracts during ovulation (118). Deviations from the normal pattern of contractions may be responsible for infertility. If the presence of secretory endometrial glands in a biopsy specimen is taken to indicate a recent ovulation, it seems that 39 per cent of the first postpartum menstrual cycles are anovular. The first postpartum ovulation occurs sooner in nonlactating than in lactating women. After complete abortion, ovulation is soon re-established, the first cycle being ovular in 75 per cent of cases, but is delayed when the abortion is incomplete (119, 120). Ovulation proceeded quite normally in 42 women who had been unilaterally ovariectomized (121). An ovary removed from a woman on the eleventh day of her cycle contained a corpus luteum estimated to be five days old (122).

Treatment with progesterone seems to induce ovulation in hens and in some mammals. But if injections are begun early in the oestrous cycle, it inhibits heat and ovulation in pigs (123), and in heifers (124). Given to heifers at the beginning of oestrus, it shortens the duration of oestrus and accelerates ovulation (125). As in rabbits and rats, atropine will delay ovulation in cows. On the other hand, it has no effect on the ovarian response to injections of chorionic gonadotrophin (126). Pentobarbital, which is also effective in blocking the release of LH^2 in rabbits and rats, does not prevent ovulation in the hen whether it is induced by progesterone or takes place normally (127).

The vascular architectural pattern of the ovary has been emphasized in a discussion of the local factors that control ovulation in the rabbit (128).

Attention is especially drawn to the extent of the ovarian lymphatic system; it is very closely connected to the veins and appears to function like erectile tissue, accommodating fluid rather than draining it away. Follicles can be made to swell and rupture by clamping the ovarian veins (but not the arteries). The pampiniform veins and related muscle fibres in the hilum of the human ovary develop at puberty and involute at the menopause. There are many arteriovenous anastomoses, and the spirally disposed arteries contain numerous epithelioid cells (129). Small vascular nerves can be identified (130), but neuroepithelial nests were not found in the hilum of the ovary (131).

Since hypophysectomy during prooestrus prevents ovulation, it has been assumed that pituitary LH is needed for ovulation. The maturing follicles present in the ovary at the time of hypophysectomy are capable of ovulating in response to the injection of LH, provided that the hormone is given within 6 hr. after the operation (132). Any ova that do ovulate are viable and develop normally after fertilization (133). Pyknosis is not often seen in the follicles until about 19 hr. after hypophysectomy, so that functional changes in viability precede morphological changes, and follicles become incapable of ovulating before the ova that they contain become unable to divide.

Reproduction in the Male

Testis and male reproductive tract.—Fewer papers have been published this past year on the male than on the female reproductive tract. Several workers have studied the damaging effects on the testes of various forms of trauma. Ischaemia, produced by ligating the testicular artery, causes damage which is proportional to the time that circulation is stopped (134, 135). Even very short periods of ischaemia injure the testis, and any interference with the testicular blood supply must therefore be regarded seriously by surgeons. The Sertoli cells survive even when all spermatogenic cells disappear. A similar condition is well recognized in the cryptorchid testis, the physiological significance of which has been reviewed by Nelson (136). Large doses of x-rays caused only temporary damage to the testis of the hamster, and spermatogonia reappeared in about eight weeks (137). β-1-Napthylalanine, an amino acid antagonist, produced nuclear vacuolation in the spermatids of mice (138). As in the ovary, multinuclear spermatogonia are frequent in the human testis for a few weeks after birth (139).

Judged on the basis of the Ashbel-Seligman reaction for carbonyl groups, tumours of Sertoli cell origin are thought to contain mainly oestrone, whereas tumours of interstitial tissue origin mostly contain androgen (140). The methods of analysis employed are, however, inadequate to demonstrate such nonketonic steroids as oestradiol, which in fact has been isolated from human testicular tissue, although in much smaller amounts than in hog or horse testes (141). It is evident from other studies dealing with the localization of lipids (142, 143) that histochemistry is still an unsatisfactory method for determining sites of hormone production.

Tepperman & Tepperman (144) show that purified FSH[2] has no effect on the cholesterol ester content of the testes of weanling rats and that very little androgen is produced. Several purified LH preparations, on the other hand, both increased the amount of cholesterol ester and the secretion of androgen. Cholesterol esters do not, however, accumulate after CG[2] has been given, although the output of androgen does increase. Prolactin has no effect. The testis can convert C^{14}-labelled acetate into testosterone and also into cholesterol (145). The addition of CG to the tissue increased the output of male hormone but did not, however, affect the incorporation of acetate into cholesterol. It is possible, therefore, that the synthetic pathway to testosterone does not involve the prior formation of cholesterol. It has been estimated that the testes of growing chicks (10 to 40 days old) secrete the equivalent of about 20 μg. testosterone propionate daily (146).

The function of the accessory organs can now be assessed by chemical estimations of constituents of their secretions, as well as by histological methods. Such methods have shown that the "female prostate" in the rat, which is active during the first few weeks of life, late pregnancy, and lactation, behaves like the ventral prostate of the male and secretes citric acid but not fructose (147). Prostatic tissue from male rats can be transplanted into females. If the host's ovaries are then stimulated with PMS,[2] the secretion of citric acid and fructose by the grafts reaches levels normally induced by androgen in the male (147). Species and organ differences in the phosphatase levels will have to be taken into account before enzyme concentration studies are used for assessing the metabolism of the accessory organs (148).

Spermatozoa.—The PAS reagent has been used in a detailed description of spermatogenesis in rodents. Four stages in the development and maturation of the acrosome are described and can be correlated with the earlier stages of spermatogenesis (149). PAS staining also reveals differences that are not apparent, using other methods, in the sperm of strains of mice with mutation-induced changes in one of the chromosomes, though the strain differences in fertility cannot be correlated with the morphological appearances (150). Other studies describe the histochemical localization of minerals, enzymes, lipids, polysaccharides, and proteins in mammalian sperm (151, 152, 153), and methods to distinguish between living and dead sperm (154, 155).

The published report of a symposium on the Biochemistry of Fertilization and the Gametes brings together much of the available information concerning the biochemical behaviour of spermatozoa and semen (156). Spermatozoa provide very convenient material for the study of intermediary metabolism, and they have been used in investigations of the process of fructolysis and the metabolism of fatty and amino acids. Unlike other tissues, they contain almost no catalase; nevertheless, under aerobic conditions they do produce H_2O_2, which is toxic to them (157). Cytochrome cannot be demonstrated in normal preparations of human spermatozoa, but the

full cytochrome spectrum can be seen if samples are frozen in glycerol to the temperature of liquid air (158). Sea-urchin spermatozoa differ from mammalian spermatozoa in that they do not obtain energy from the medium in which they live, for they are capable of prolonged activity in pure sea water. The small amount of sugar they contain and their high energy requirements suggest that the breakdown of phospholipid and not of carbohydrate provides for their needs (159).

The quantity of seminal fluid, and hence the concentration of spermatozoa and the amount of substrate available, varies widely from one species to another. It is, therefore, important to consider not only the concentration of substances in the ejaculate but also the total amount. Further studies have provided estimates of the amount of fructose in the semen of seven breeds of cattle (160). The semen of boars contains a high proportion of inositol (161), and also ergothioneine (162). Since these and other substances in the semen are secreted by the secondary sex organs, in amounts which vary with the quantity of circulating male hormone, chemical analysis of the semen can be used for the assay of androgenic extracts and also to assess androgen output in men (163).

Gonadotrophins

Unfractionated pituitary gonadotrophin given to cows early in oestrus reduces the interval between the end of oestrus and ovulation (164) without altering the duration of oestrus. The calf's ovary is sensitive to horse anterior pituitary extract as early as one week after birth, and ovulation can be induced at the age of three weeks by means of combined LH and FSH treatment (165). The subsequent development of superovulated eggs depends on the time in the cycle when gonadotrophin is injected. Five heifers treated during the luteal phase were artificially inseminated, and it was found that none of 34 eggs ovulated had been fertilized and that all the animals had pyometra. On the other hand, of five heifers treated during the follicular phase, none developed pyometra, and 32 of 43 eggs underwent cleavage (166).

Large doses of chorionic gonadotrophin may induce ovulation in women (167). Decidual changes are stimulated, and the Berger cells of the ovarian hilus are also activated (168). Menstruation is delayed but takes place three or four days after the end of treatment.

Amounts of sheep pituitary FSH large enough to cause detectable changes in the uterus and other secondary organs of immature mice have only slight morphological effects on the gonads (169). Small doses of PMS given to mice also induce changes in the nuclei of the stromal cells of the uterus; this effect suggests the production of progesterone, although no obvious thecal changes occur and no corpora lutea develop (170). The reproductive organs of the bat respond to PMS or CG in the same way as those of the rat, but seem less sensitive. During hibernation bats are said to be in prolonged oestrus and can be made to ovulate by means of PMS or CG (171). Mam-

malian gonadotrophin can stimulate the secretion of androgen in hypophysectomized cocks for a limited period only. A preparation of chicken pituitary, however, can maintain growth of the comb for a long period (172).

There is general agreement that large doses of oestrogen suppress the secretion of gonadotrophin, but there is still doubt about the effects of smaller, and presumably physiological doses. Byrnes & Meyer (173) consider that very low doses decrease the secretion of FSH, and that LH production is increased at rather higher dose levels. The pituitary becomes less sensitive to oestrogen as maturity is reached. It has often been suggested that non-oestrogenic derivatives of oestrogens are responsible for stimulating the pituitary; a highly oxygenated carboxylic acid which has this effect has been isolated from dilute aqueous alkaline solutions of stilboestrol (174). The monobenzyl ether of stilboestrol is only weakly oestrogenic but it, too, seems able to stimulate the pituitary. It has been used successfully in the treatment of patients with amenorrhoea (175).

Fertilization

Phase-contrast microscopy permits very detailed observations to be made on living gametes before, during, and after fertilization. The formation of the second polar body in the rat ovum has now been described (176), and the earliest stages of fertilization, the development of the pronuclei and their conversion into prophase chromosomes have also been studied and photographed (177, 178). There is still no convincing evidence that complete fertilization has been effected *in vitro*. Some of the apparent successes may be explained by parthenogenetic changes or degenerative fragmentation resembling cleavage (179). Successful fertilization in Fallopian tubes, kept *in vitro* and containing ovulated ova and added sperm, has been attributed to anaerobic conditions, and perhaps the presence of tubal secretion (180). Fertilized ova have been washed out of the Fallopian tube of a heifer that had been given a superovulating dose of gonadotrophin and then artificially inseminated. An eight-celled ovum was transplanted successfully into another heifer (181). Sperm are normally present in the Fallopian tube before the ova, and it seems that the capacity for fertilization is increased during the "waiting interval" (182).

The process of fertilization has been best studied in echinoderms, particularly in the sea urchin. A recent review by Rothschild deals with the morphology, movement, and metabolism of sea-urchin spermatozoa. It also discusses the gamone substances and the phenomena of agglutination, matters whose relationships to problems of mammalian fertility are still obscure (183). There is no evidence that chemotaxis of sperm to eggs occurs during the process of fertilization in mammals. But chemotaxis does seem to occur in ferns and mosses, and also takes place between seaweed gametes (184). Dilute simple hydrocarbons, e.g., *n*-hexane, will simulate the chemotactic properties of cell-free preparations from the eggs (185).

It has been known for some time that hyaluronidase can disperse granu-

losa cells surrounding the egg. It now appears that the cumulus around the ovum does not disappear until after fertilization occurs, so that the part played by hyaluronidase in fertilization remains obscure. Administration of the enzyme to sterile women through the cervical canal proved an unsuccessful method of treatment, nor could hyaluronidase be found in the tubes after such treatment (186). On the other hand, experiments seem to suggest that mucopolysaccharides, which may be related in some way to the hyaluronidase system, reduce fertility. Thus it was shown some years ago that derivatives of hyaluronic acid inhibit the dispersal of cumulus cells *in vitro* and can act as contraceptives (187), presumably by providing an alternative substrate for the enzyme. The differentiation of the fertilization membrane is also prevented when eggs are fertilized in the presence of mucopolysaccharides, including heparin (188). Phosphorylated hesperidin is a strong but nontoxic inhibitor of hyaluronidase. Given either intraperitoneally or orally it had no effects on male rats or on the oestrous cycle of females. But only very few of the treated rats gave birth to litters (189).

An improved method of extracting the active principle of *Lithospermum ruderale* is reported (190). The extract contains a water-soluble oestrogen, and when injected into animals causes involution of the gonads and thyroid. It is possible that this effect is due to the combination of circulating trophins with phlebotannins, also present in the extract, to form inactive colloidal complexes. As the extract also led to an increase in the size of the adrenals and a decrease in that of the thymus (191), an alternative explanation is that the suppression of the gonads and thyroid is part of a stress response. An argument against the first explanation is the fact that the activity of lithosperm is destroyed by heating, a procedure which does not affect the tannins (192). When incorporated in the diet in quantities not quite sufficient to cause permanent dioestrus, lithosperm diminished the incidence of spontaneous mammary tumours in a susceptible strain of mice (193).

Fertility

Paradoxically, while the total world population continues to increase at an alarming rate, it is the problem of infertility which exercises most students of reproduction. General reviews of the problem (194, 195) do not seem to indicate that any major advances in treatment are on the horizon. None of factors that have been suggested, such as ill-health, uterine displacement, or bacterial infection, seems to be responsible for inadequate cervical mucus which, it is generally conceded, may prove a barrier to conception (196). Treatment with oestrogens was much more successful in restoring the mucus to normal than the administration of antibiotics.

Obesity in women is often associated with sterility, but obesity induced in rats by hypothalamic lesions is not necessarily associated with changes in the sex cycle (197). Such obese rats may, however, refuse to mate.

There have been few advances in the therapeutics of male infertility during the past few years. On the other hand, the criteria used to assess the

fertilizing power of a sample of human semen have become less exacting. Studies of large groups of fertile and nonfertile men (198, 199, 200) reveal that fertility is not correlated with sperm count when the count is above 20 million/cc. It seems to be more positively related to sperm motility, and to the proportion of sperm that are morphologically normal. Enhanced motility may often compensate for a low total count and should be taken into account in discussing sperm quality (201, 202). Methods for estimating this motility and its dependence on such factors as pH, osmotic pressure, and electrolyte concentration have been described (203, 204, 205).

Preservation at low temperatures seems to be more successful with sperm than with ova. Present methods are satisfactory for storing sperm for only a few days; yet the time may soon arrive when sperm can be stored long enough for progeny testing to indicate the value of different sires. Mammalian sperm are more difficult to store satisfactorily than are avian sperm (206, 207).

Discussions on problems of fertility in farm animals, particularly cattle (208, 209), have emphasized the importance of mineral salt-ratios in the diet, especially the Ca:P ratio. Variations that occur in the sexual behaviour of animals are described in one of the volumes of the Ciba Colloquia (210).

Pregnancy

Records relating to 15,659 women have been used in an analysis of the duration of unusually long pregnancies. Seven pregnancies are said to have lasted longer than 48 weeks, the longest of all being 359 days, a fact which has some medico-legal importance. Excluding the unreliable records, and taking five days as the minimum possible interval from the onset of a period to the time of ovulation, the five longest estimates are 319, 320, 321, 325, and 328 days (211). The duration of pregnancy in the horse is independent of the level of nutrition, but varies according to the time of the year when breeding takes place, being 10 days longer in the first half of the year (212).

Although it is usually supposed that the vaginal membrane is closed throughout pregnancy in the guinea pig, it often opens at about the twenty-sixth or twenty-seventh day of gestation, and remains open for several days (213). The suggestion is made that the closure membrane disappears during a period when the production of progesterone by the corpus luteum declines, and before the placenta takes over. The injection of progesterone shortens the duration of the period of opening.

The first pregnancy in mice is characterized by the disappearance of the X-zone of the adrenal cortex, the change beginning about two days after implantation. This cortical region is unaffected by the administration of oestrogen or progesterone, or by pseudopregnancy, but disappears when androgen is given. When dividing ova are grafted into the anterior chamber of the eye, trophoblastic tissue grows, and the X-zone disappears, provided that corpora lutea are present. It is suggested that they produce an androgen (214).

The amount of progesterone necessary to maintain pregnancy varies widely from one species to another. In heifers, 25 mg. daily is inadequate and 75 mg. usually adequate, in the early stages of pregnancy (215). About 10 mg. daily is needed by the pregnant goat. Normally the ovaries seem to secrete more progesterone than is required, for some of the corpora lutea can be removed without interrupting the pregnancy (216). Pyridoxine-deficient rats seem to suffer from an hormonal deficiency very similar to that which follows the removal of the pituitary and ovaries (217). They can be kept pregnant to the seventeenth day if given 4 mg. progesterone together with 1 μg. oestrone daily. The implantation of six 25-mg. tablets of progesterone enabled 72 per cent of 85 women with a history of two or more miscarriages to come safely to term (218). In the mink, implantation is normally delayed. Exposure of the animals to added light reduces the delay, which is unaffected by progesterone (219).

In rats pseudopregnancy normally follows a sterile mating. Any vigorous, nonspecific "stress," such as epinephrine, formaldehyde, and tissue homogenates, will cause the release of sufficient LH to provoke the condition (220). The anoestrus that follows adrenalectomy is also said to be a pseudopregnancy, and not due to ovarian or pituitary failure. In this instance, however, it is not a nonspecific result of surgery or anaesthesia. On the contrary, the removal of the adrenals does away with some specific inhibition of the pituitary and permits the release of LH (221). Adrenalectomy is also said to facilitate the appearance of deciduomata (222). The duration of pseudopregnancy induced by deciduomata varies directly with the amount of trauma (223). Successive sets of deciduomata can be obtained provided that enough progesterone is given (224). A perfect decidual reaction which reproduces the changes that occur around an implanting ovum requires the synergistic action of oestrogen, progesterone and vitamin E (225).

The placenta.—Placentation in the very uncommon Père David's deer, which today survives only in zoos, has been described (226), and a study has been made of the gradual process of attachment of the bovine blastocyst (227). The placental giant cells in ruminants are derived from the trophoblast and seem to be related to the syncytial trophoblast cells of deciduate placentae (228). The arrangement of the villi and the relations of maternal vessels to intervillous spaces in the human placenta have also been described (229).

Transplants of full-term human placenta have been maintained in the anterior chamber of the eye of rabbits for a period of four to six months (230). Langhans cells grew and produced a hormone with effects similar to those of CG, while the appearance of the uteri of spayed rabbits that had received grafts suggested that the syncytial cells might be secreting oestrogen. There was no clear evidence that progesterone was being produced. The placenta of the rat does not produce enough oestrogen or progesterone to take over the secretory functions of the ovary. On the other hand, it seems to contain prolactin (231). There is evidence that the human placenta contains ACTH[2]-

like material (232), though this observation has also been denied (233).

An important book, *Antibodies and Embryos* (234), summarizes the investigations of Brambell and his colleagues on the physiological properties of the placenta in relation to immunity reactions and to the transfer of large sized molecules between mother and foetus.

Intrauterine death of foetuses.—According to the Report of the Royal Commission on Population (235), spontaneous abortion occurs in 7 to 11 per cent of all pregnancies. The proportion of abortions caused by defective germ plasm and by a defective environment, which may be amenable to treatment, is not known. Consequently, it is necessary to try to salvage the conceptus in all cases of threatened abortion. Uterine malformations have been found in 20 per cent of women suffering from habitual abortion (236), and anomalies of the chorionic villi occur in 38 per cent of spontaneous abortions (237). The abortion rate was twice the normal rate in 291 women who became pregnant after a period of sterility lasting at least two years (238). Evidence about the extent to which the foetuses of farm animals die *in utero* continues to accumulate. In one study the number of lambs born represented only 40.2 per cent of the total eggs ovulated, and the death rate of implanted embryos was 24.3 per cent (239). In pigs, the latter rate was 25 to 38 per cent (25), and surprisingly was lower in poorly-fed animals.

Now that Rh-*iso*-immunization is recognized as a factor responsible for the loss of human foetuses, attempts are being made to induce the condition experimentally or to demonstrate its natural occurrence in other mammals. Haemolytic disease could not be produced in foetal rabbits by immunizing the mother with the father's blood (240), while a haemolytic reaction in foals is not manifest until the ingestion of colostrum has allowed maternal immune bodies to enter the foal's circulation via its intestinal wall (241). There is some evidence that a similar condition may occur in pigs (242). Bacterial antibodies do not cross the placenta in cows, and haemolytic disease in calves is therefore unlikely, though sensitization of red blood cells by colostral antibody, as mentioned above, might occur. In herds with high abortion rates, there was an increase in the proportion of cows' sera reacting against the blood of the bulls with which they had been mated (243). A gene-conditioned recessive sterility has been reported in one line of Jersey cows. There were no apparent abnormalities in the reproductive tracts, in ovulation or cell division, but the eggs die at a later stage, presumably from difficulties in implantation (244). Large hereditary differences in the ability to conceive have also been reported in mice that mate successfully (245).

Hereditary and environmental factors which influence the development of foetal malformations have been reviewed by Penrose (246). Besides the well-recognized causes of foetal death or abnormality, such as virus infections of the mother early in pregnancy or the *iso*-immunization phenomenon, other substances causing foetal loss have been described. Thus progesterone given on the sixteenth to twentieth day of pregnancy causes foetal death in mice, and very small amounts are toxic to baby mice during the first few

days of life (247). Cortisone, too, has produced resorption and abortion of the young in rabbits (248). Given to rats early in pregnancy it had no effect, but large doses given during the midterm killed the foetuses (249). Cortisone and ACTH have a similar effect in ovariectomized mice whose pregnancy is maintained by progesterone (250). The effect cannot, therefore, be via the ovaries. ACTH also caused congenital deformities of rats' legs (251). Cortisone given therapeutically, in the hope that it would inhibit immunity reactions, failed to prevent the development of erythroblastosis (252).

Sex ratio of foetuses.—Assuming that spermatozoa bearing *x* or *y* chromosomes occur in equal numbers and are equally viable, and that the zygotes of the two sexes are equally viable *in utero*, both the primary sex ratio (at conception) and the secondary ratio (at birth) should be 100:100. Nothing is known about the primary ratio in mammals, and it is clear that in man the secondary ratio, 105.6 male to 100 female is significantly different from equality. Surveys have recently been made of the sex ratios in all births (live and still) occurring between the fortieth and the twenty-eight weeks of pregnancy, when births become statutorily notifiable in England, and it appears that the younger the pregnancy the more unbalanced the sex ratio becomes in favour of males (i.e., the higher the sex ratio) (253). It has also been found that the sex ratio of single stillbirths increases, whereas that of twin stillbirths decreases with maternal age (254). Further, the sex ratios of stillbirths differ according to the cause of the stillbirth, the frequencies of these causes themselves varying with the age of the mother (255). These observations indicate that the global sex ratios are compounded of a number of individual sex ratios which may vary widely, one component of the total often swamping the contribution of smaller items. Such variations make it impossible to extrapolate the observed sex ratios into earlier intrauterine life, and reliable information about the sex of abortuses (i.e., foetuses younger than 28 weeks) is unavailable. Even so, it is quite clear that there are differences in the viability of male and female zygotes, and that the differences are probably not constant throughout pregnancy.

Statistical studies by Waterhouse & Hogben (256) show that compared with O×A families, there are fewer families with parents A×O and fewer children in such families than is expected, resulting almost entirely from selective loss of group A children. These workers estimate that there are about 25 per cent fewer A children than would be expected from A×O marriages, and they also show that the proportion of A children to O children declines as the number of pregnancies increases. The responsible factor may be either an increasing titre of an anti-A substance in the mother or increasing placental permeability to an immune body.

Differentiation of reproductive tract.—The differentiation of the gonads and of the accessory reproductive organs was discussed in last year's *Annual Review of Physiology*, in a chapter which summarized the material provided at a colloquium in Paris (257). The development of the gonads has also been reviewed recently by Witschi (258), and there is little new to report now.

Our understanding of the genesis of the freemartin in cattle has not progressed, and it is useful therefore to refer to some data which may bear indirectly on the problem. It has been shown that skin grafts can be exchanged between twin calves, one of which is a freemartin, despite their undoubted genetic dissimilarities at conception (259). Some years ago Owen reported that though there are about 40 separate blood-group factors in cattle, the majority of nonidentical twins have identical blood groups, and in certain special circumstances of superfecundation, had groups that could only have come from the other twin (260). Similar findings have been reported in quintuplet calves (261), where the bloods of one heifer and four bull calves, developed from separate eggs, contained identical cellular antigens in constant proportions. These findings indicate that there is a transfer of blood cells from one foetus to the other; that descendents of these cells continue into adult life; and that the twins are to some extent genetic mosaics. If one type of cell can be transferred in this way, it is not inconceivable that early germ cells might also migrate from one embryo to the other. If they did, the male gonocytes from one embryo might possibly induce male changes in the female gonadal anlage of its twin.

Hypothalamus and Reproduction

It is usually assumed, in discussions of the "stress syndrome," that an increased demand for ACTH is associated with a "pituitary shift" from the production of gonadotrophin. Evidence is, however, accumulating which shows that increased amounts of gonadotrophin as well as of ACTH may be produced in some conditions of nonspecific stress. Thus both the ovaries and adrenals hypertrophy after tissue homografts (262), and nonspecific stresses may accelerate the time of onset of puberty (263). Prolonged electrical stimulation of the cervix in young rats, a stimulus which would certainly seem to fall within the definition of stress, also accelerates puberty (264). This effect can be inhibited by large doses of Dibenamine [*N*-(2-chloroethyl) dibenzylamine].

This experiment also suggests that a neural mechanism is concerned in the release of gonadotrophin from the pituitary. A neuro-endocrine reflex, depending on local afferent pathways from the ovary, is postulated by Aron, Marescaux & Petrovitch (265), in explanation of the results of certain experiments dealing with compensatory hypertrophy of the ovary. Unilateral hysterectomy, however, causes similar hypertrophic changes in the ovaries without interfering with their innervation (266), so that the findings of Aron and his co-workers could also be explained in terms of the release of gonadotrophin after the general stress of an operation, rather than of excitation of a specific reflex pathway.

The possible control of the anterior lobe of the pituitary by the hypothalamus continues to stimulate discussion, and the results of stalk-section continue to be very contradictory. Greep & Barrnett (267, 268) now report that after complete section of the stalk, the gonads become underactive

rather than completely inactive. They think that this finding is due to ischaemia of the anterior lobe, with subsequent cellular degeneration. They did not observe any regeneration of portal vessels in the cut stalk.

Thyroid and Reproduction

Observations about the influence of the thyroid on reproductive processes continue to conflict with each other. Sexual maturity can apparently be induced in young female mice by treatment not only with thyroprotein but also with thiouracil (269), while treatment of the pregnant mouse with I^{131} impairs subsequent reproduction in the female but not in the male embryo (270). On the other hand, surgical thyroidectomy had no consistent effect on any stage of reproduction in female rabbits (271), nor was the fertility of male guinea pigs affected either by thyroidectomy or thyroxine administration (272).

Maqsood (273, 274, 275) has tried to find out how important the thyroid is for the maintenance of normal fertility in the male rabbit. Thyroxine in physiological doses seemed to stimulate spermatogenesis and libido, and there were also indications that it could induce precocious puberty. Treatment with thiouracil had the reverse effect. The suggestion from these experiments that thyroxine should be of value in the treatment of male infertility, accords with a widespread clinical opinion, for many observations appear to suggest that thyroid dysfunction in man is associated with disorders of reproduction, although the relationship is far from clear-cut (276). Signs of hypothyroidism are reported in cryptorchidism, and thyroxine may help such cases (277).

Experiments on female guinea pigs suggest that the placenta is permeable to thyroxine and thiouracil but not to thyrotrophin (278). These facts are important in relation to the treatment of hyperthyroidism in pregnancy (279). It should be remembered that Brambell's work has demonstrated very clearly that the placenta is selective in allowing or refusing the passage of antisera according to the species from which they were derived. This selectivity may extend to foreign protein hormones.

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COMPARATIVE PHYSIOLOGY OF INVERTEBRATE ENDOCRINES[1]

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Hormone mechanisms in invertebrates show a remarkable parallelism with those of vertebrates (see 14, 15, 16, 18, 27, 37, 66, 141, 142, 146, 173). Much of the recent progress in invertebrate endocrinology concerns (*a*) investigations of the central nervous system as a source of hormones, and (*b*) efforts to understand hormone effects in terms of cellular chemistry. In reviewing these trends against a background of the major known results, the author found it necessary not to limit herself to the period covered in this volume but to include work published prior to 1951.

Crustaceans

Important functions controlled by hormones are color change, retinal pigment migration, growth and molting, metabolism, reproduction, and perhaps development and maintenance of secondary sex characters (reviews: 13, 14, 15, 16, 18, 55, 85, 112). Metabolic changes observed after interference with the normal endocrine pattern concern sugar, calcium, phosphorus, water, and rate of oxygen consumption. Some of these activities are interrelated and are controlled by additional nonendocrine factors. The resulting complexity is the reason why certain effects observed after experimental interference with the endocrine system, such as the alteration of heart rate (69), of locomotor activity, and of "viability" (51), are not yet clearly understood.

In crustaceans, hormones are present in certain parts of the central nervous system including the *x* organ, in the sinus gland, and perhaps in the gonads. Since implantation of the sinus gland showed it to contain molt-inhibiting, metabolic, and chromatophorotropic hormones, its role as the place of origin of these substances seemed well established. The function of the *x* organ (44) remained obscure for 20 years following its discovery by Hanström (65). A combination of physiological and histological methods and the adoption of concepts recently developed in vertebrate and in insect endocrinology led to a re-evaluation of the role of the sinus gland and an understanding of the function of the *x* organ. The sinus gland and the *x* organ are not separate endocrine structures, but must be considered as components of a neuroendocrine system (10, 70, 113, 114, 115, 172, 177). Some of the hormones present in the sinus gland are produced in the neurosecretory cells of the *x* organ and transported via their axons to the sinus gland where they are stored. Besides the *x* organ other parts of the central nervous system containing neurosecretory cells are hormone sources. There is evidence that

[1] The survey of literature pertaining to this review was concluded in July, 1952.

some of these active principles too are stored, either in the sinus gland or in comparable structures characterized by an aggregation of colloid-bearing nerve terminals.

The hormone actions most extensively studied concern the control of physiological color change. Among the crustaceans, different types can be classified according to the character of their pigmentary responses, the variety of which cannot be explained in terms of a single chromatophorotropic hormone. According to the "multiple hormone hypothesis" (18) present evidence indicates the existence of at least five distinct chromatophorotropic principles. These can be differentiated not only by their specific effects on certain types of chromatophores, but also by their distribution in the organism [three in the sinus gland, two in the central nervous system (135)] and, to some extent, by their solubility in alcohol (19, 24). As in other arthropods, for example *Limulus* (140), the distribution of chromatophorotropins in the central nervous system of crustaceans can be correlated with the occurrence of groups of neurosecretory cells (53, 54, 88).

The release of these hormones into the circulation depends on various factors, such as degree of illumination, nature of background, and sequence of light and dark periods (diurnal mechanism), which in certain crustaceans results in a persistent daily rhythmicity of pigment distribution. This inherent rhythm continues for some time independent of external conditions, for instance if animals are maintained in constant darkness. The 24-hr. periodicity can, however, be altered by certain experimental procedures. Constant illumination finally leads to the disappearance of the rhythm; illumination at night followed by darkening during daytime results in reversal of the rhythm (22, 25). In contrast to opinions held formerly, it is now known that different types of chromatophorotropins may interact so that the response of a given pigment to one hormone is concentration, to another dispersion of the pigment (21, 22, 176). Effects antagonistic to those of a given chromatophorotropin may also be brought about by nonhormonal substances (33, 52). Thus, an enzyme whose effect cannot be duplicated by other tested enzymes acts as a pigment-dispersing factor by either inhibiting or destroying a concentrating hormone (32).

The active principles controlling retinal pigment migration, a dark-adapting and a light-adapting substance (17, 20, 23, 107), are present in the central nervous system and in the sinus gland, and are in all probability not identical with any of the known chromatophorotropins. Responses of the crustacean retinal pigments are, to a large extent, conditioned by external factors. In addition to dependency on light intensity, background (136, 137), temperature, etc. there exist diurnal rhythmic patterns (175). The differential production of the two hormones regulating the distal retinal pigment of *Palaemonetes* can be experimentally controlled by the administration of light of varying intensity over varying periods of time (26). In *Leander*, for example, light seems to sensitize the distal pigment cells of the compound eye to the hormone by which they are activated (87).

In the control of molting and growth two hormones are involved. The existence of a molt-promoting factor can be demonstrated in *Lysmata* by the increase in the molting rate of winter animals (which normally have longer intermolt periods) that receive extracts prepared from eyestalks of more frequently molting summer animals (31). A molt-inhibiting factor safeguards "quiescent" periods in species with seasonal molting behavior. Its absence in eyestalkless test animals leads to changes characteristic of the premolt period (resorption of calcium from the exoskeleton and its deposition in the body as gastroliths, increase in water content and oxygen consumption). There is evidence that both hormones originate in neurosecretory cells of the *x* organ and of other parts of the central nervous system. For the molt-inhibiting hormone this has been worked out in some detail (10, 70, 113, 114). Precocious molting occurs in crabs after surgical removal of the *x* organs, but not after extirpation of the sinus glands. On the other hand, molting in eyestalkless animals can be delayed or inhibited by the implantation of either *x* organs or sinus glands. Neurosecretory cells of the kind forming the *x* organ [β cells of Enami (54)] likewise occur in the brain and in the commissural ganglia, organs which inhibit molting after implantation into eyestalkless test animals (160).

Hormone controlled changes in metabolism are, in part, associated with the molting cycle. In the absence of the metabolic principle (or principles) the rate of oxygen consumption rises and the respiratory quotient falls (10, 51, 57). Although these effects can be prevented by the implantation of sinus glands into eyestalkless animals, the same effects can be elicited by sinus gland removal only temporarily, if at all (10). Similar differences between the effect of eyestalk removal and that of sinus gland extirpation were also observed in studies concerned with the calcium and phosphorus content (70, 92, 172). All these results support the view that the active principles involved originate in the neurosecretory *x* organ and are stored in the sinus gland. It is not known whether or not the factor controlling blood sugar levels which is present in the sinus glands of a number of species (86, 106, 151), might also be produced by neurosecretory cells of either the *x* organ or the brain. This would seem possible in view of the observation that hyperglycemia induced by epinephrine in *Callinectes* may be mediated by structures outside of the eyestalk (86). Another metabolic effect concerns a "protein-astacine complex," an integumentary pigment of the carotenoid type whose split products cause reddening in eyestalkless *Carcinus* (95).

Reproduction is controlled by a sinus gland factor which seems to be different from known chromatophorotropins (167). Eyestalk removal results in acceleration of egg development (103), even in immature females (45). Eyestalk extracts inhibit ovarian growth; similar effects are observed with extracts of brain but not of thoracic ganglia (103). A detailed study of the endocrine control of the ovary of *Cambarus* in connection with seasonal conditions was undertaken by Stephens (161), who interpreted her results by a theory at variance with the views held by other investigators regarding the

relationship between neurosecretory cells and sinus gland. The complex mechanism safeguarding periods of reproductive quiescence under unsuitable conditions is still rather obscure. An endocrine relationship between sinus gland and gonads is also made probable by the observation (80) that degeneration of the gonads of parasitized crabs is paralleled by an enlargement of the sinus glands.

The presence of sex hormones in crustaceans is suggested by a number of observations, but final proof is still lacking. The available evidence concerns mainly the effect of castration on secondary sex characters. Surgical gonadectomy (164, 166) or irradiation by x-rays (165) did not affect permanent sex characters of the isopod *Armadillidium* and thus gave no indication that sex hormones are present in its gonads. Changes in the sexual dimorphism after destruction or modification of the gonads by irradiation or by parasites were, however, repeatedly observed in a variety of higher crustaceans. Newer contributions dealing with "parasitic castration" (38, 129, 131) confirm the observation that different species, and even different individuals, vary greatly in the response of their secondary sex characters to the presence of parasites. As a rule, the effect of parasitism is more pronounced in males with the secondary sex characters changing to resemble those of the female (80). The observed effects are interpreted by some investigators on the basis of metabolic changes in the host caused by parasitism and resulting in sex inversion (130) or in hyperfeminization (38, 129), and do not necessarily require the postulation of sex hormones for their explanation. However, this interpretation does not account for the appearance in females of transitory sex characters which are important in the care of the young, and which seem to be controlled by a humoral factor furnished by the ovary (36, 129). On the other hand, eyestalkless animals with functional ovaries lacked signs of "feminization" at the puberty molt (39), and irradiation with x-rays showed no relationship between the condition of the ovary and the development of the brood sac (165).

Insects

Growth and differentiation, reproductive and metabolic processes, and color adaptation are under endocrine control. The question of the presence of sex hormones in this group of invertebrates is still undecided (reviews: 43, 74, 104, 141, 142, 146, 179). The most versatile organ of internal secretion is the neurosecretory component of the central nervous system (34, 48, 97, 98, 147, 154, 162, 171, 180, 181). Other known sources of insect hormones include the corpora cardiaca and allata (4, 5, 67, 82, 94, 96, 105, 133, 138, 156, 171) and the prothoracic glands (and their homologues; 41, 42, 82, 125, 126, 143, 156, 158). The neurosecretory cells of the brain, together with the corpora cardiaca and allata form a neuroendocrine system (147), whose components show changes when the connecting pathway is severed (145, 148). The cytological features of some of these endocrines suggest secretory cycles paralleling functional states (48, 98, 127, 128).

The interaction of various hormones involved in insect reproduction is

not yet fully understood. The organs of internal secretion controlling reproductive processes, particularly in the female, are the corpora allata, the neurosecretory cells of the brain, the corpora cardiaca, and possibly the gonads. The role of the corpora allata in egg maturation and in the secretory activity of accessory sex glands described by earlier observers was confirmed (2, 111). The corpora allata seem to be controlled by endocrine [allatotropic hormone? (170)] and nervous factors (148). In *Anisolabis* the brain is said to exert a stimulatory and the stomachic ganglia an inhibitory influence on the corpus allatum (111). The nature of these mechanisms, as well as the question of whether the corpus allatum hormone is a specific gonadotropic or metabolic principle, need further study.

Egg development did not occur in young adult females of *Calliphora* when the medial neurosecretory cells (pars intercerebralis) were extirpated (170). Implantation of neurosecretory cells in animals from which these cells had been previously removed furthered egg maturation. Control experiments with portions of the brain not containing neurosecretory cells had negative results. Since the removal of the neurosecretory cells interrupted egg development at an earlier stage than did allatectomy, the observed effect must be considered as primary and not, or not exclusively, as indirect, i.e. via the stimulation of the corpora allata. According to Thomsen (170) the nature of this hormone effect seems to be general rather than specifically gonadotropic. In this connection, the observation that the neurosecretory cells of the brain of newly emerged phasmids show practically no signs of secretory activity, while these cells are most active at the time of egg deposition, is of interest (48).

Flies deprived of their medial neurosecretory cells could develop their eggs, if they received implants of corpora cardiaca taken from mature females (170). On the other hand, absence of the corpus cardiacum in females possessing neurosecretory cells as well as corpus allatum did not prevent egg maturation. In the opinion of the reviewer these results can be explained by postulating that the corpus cardiacum does not itself produce a gonad-stimulating hormone, but that it stores hormone-containing neurosecretory material which it receives via the axons of the nervi corporis cardiaci (p. 467).

Although the presence of sex hormones in insects has not been definitely proved, there are indirect indications for the production by the gonads of physiologically active principles. Thus in certain species the corpus allatum hypertrophies after castration, the imaginal discs of *Drosophila* develop better in hosts containing normally functioning ovaries, and sex differences in tumor mortality in *Leucophaea* are not observed after castration (see 146). Injections of extracts from the ovaries of queen bees stimulate sterile ovaries of workers to produce eggs (1, 2). The active substance involved is water-soluble, heat-labile, and bound to a protein. Since comparable effects can be elicited with extracts of other organs of queens, such as the corpora allata, the classification of the ovarial substance as a sex hormone is open to question.

In insects, as well as in other arthropods (93), the rate of embryonic development is controlled by various factors, predominantly temperature and light. The silkworm, for instance, shows a marked rhythm characterized by periods of developmental arrest (diapause). Depending on the race, uninterrupted generations (nondiapausing summer eggs) may alternate with dormant generations (diapausing winter eggs). A recent series of investigations (58 to 62) demonstrates that this voltinism is controlled by an endocrine factor furnished by the subesophageal ganglion. Since this ganglion contains neurosecretory cells, they can be assumed to be the source of the "diapause factor." Implants of subesophageal ganglia, but not of brains or prothoracic ganglia, in silkworm pupae destined to produce nonwintering eggs, induced the deposition of wintering eggs by the resulting moths. There is evidence that the release of the diapause factor by the subesophageal ganglion is under the nervous control of the brain.

Concerning the role of hormones in postembryonic development (molting and metamorphosis) many details have been recorded (see 146) which seem to indicate a great variety of possible mechanisms. Attempts have been made from time to time to evaluate observed facts so as to arrive at an explanation which applies to insects in general. An interpretation (146, 149), which takes into account the developmental processes in holo- and hemimetabolous insects alike, but which has not remained undisputed (109, 110), has evolved from a theory originally proposed by Wigglesworth (178, 180, 181, 183). According to this concept, which is reviewed here in the light of recent information, postembryonic development is controlled by two interacting hormone systems. The one promotes growth and imaginal differentiation and leads to molts coupled with metamorphic changes. The other ["juvenile hormone" (178)] furthers the maintenance of immature (larval or nymphal) characters and thus counterbalances the action of the first hormone system. One of the functions of the juvenile hormone is the control of the instinctive behavior leading to the spinning of the cocoon in lepidopterans (120, 174).

As to the first-named hormone system, one disturbing fact was the seemingly different endocrine capacity of the lepidopteran brain, which was known to act by way of the prothoracic glands (76, 77, 78, 154, 185, 186, 187), and that of the brain of other orders of insects, where it appeared to act directly on the effector organs. The discovery of the presence of prothoracic glands (or their homologues) in a variety of insect species, and the demonstration that their physiological activity parallels that of the homologous organs of lepidopterans (46, 99, 100, 117, 121, 124, 125, 126, 143, 158, 182, 183), now permits the formulation of a tentative generalization: The prothoracic glands (pericardial, ventral, peritracheal glands, lateral ring gland cells, intersegmental organs) are the source of the hormone which promotes growth, molting, and imaginal development, and also causes the maturation of pupal spermatocytes (123, 185). The release of this hormone for which the term "growth and differentiation hormone" has been proposed (149) is brought about by an endocrine stimulus from the neurosecretory cells of the

brain. This tropic factor was called "prothoracotropic hormone" (147). One further point of interest concerning this principle is its storage in the corpus cardiacum (p. 467). The production and release of the prothoracotropic hormone by the neurosecretory cells of the brain depend on various factors. The timing of developmental events, especially the diapause, a period of developmental arrest (3, 77, 185), is conditioned by temperature; in *Rhodnius* the neurosecretory cells are activated by nervous stimulation [expansion of the abdomen following a large meal (178)].

With this information available it is now possible to summarize the events taking place in the course of insect development as follows: In response to a nonendocrine, such as a nervous stimulus, the prothoracotropic hormone is released either from the neurosecretory cells of the brain which produce it, or from the corpus cardiacum which stores it. It triggers the prothoracic glands (or homologous structures) which in turn give off the growth and differentiation hormone. This principle acts on the effector organs which respond with changes leading to imaginal differentiation, unless the juvenile hormone is present in the circulation at the same time (12, 63, 75, 119, 126). The interaction of both developmental hormones results in larval (or nymphal) molts while the presence of the growth and differentiation hormone alone (as in allatectomized animals) leads to metamorphosis. In this way periods of growth are accomplished without the intervention of precocious adult development. Once the insect has reached appropriate size and stage, the completion of development takes place presumably in the absence of a sufficient amount of juvenile hormone. In connection with this view, it is of interest that the size ratio of corpora allata and prothoracic glands in lepidopterans changes from 1:2 to 1:29 during postembryonic development (82).

The question arises why the stimuli initiating a molt (such as the nervous stimulus in the case of *Rhodnius*) do not act on the prothoracic glands directly but through intervention of the glandular portion of the brain. A possible explanation was given in analogy with the concept of the general significance of neurosecretion developed for vertebrates (see 147), according to which the neurosecretory cells in their dual capacity as nerve cells and gland cells act as mediators between the two systems of integration (see also 185).

The influence of the corpus allatum on the metabolism of adult insects is evident from the fact that in *Calliphora* allatectomy decreases the oxygen consumption while implantation of corpora allata increases it (169). Older observations concerning the hypertrophy of the fat body following allatectomy were confirmed (170). Furthermore, the removal of the neurosecretory pars intercerebralis results in scanty fat and abundant glycogen deposits in the fat body. The pericardial cells, whose endocrine nature has not been established and which should not be confused with the pericardial glands (171), possibly play a role in the intermediary protein metabolism of *Panorpa* (157).

Physiological color adaptation is restricted to a small number of insect species. Recent contributions are mainly concerned with the origin of chromatophorotropins in the insect body. The most important hormone source

is the brain. Its extirpation in *Carausius* inhibits color adaptation, its implantation or the injection of brain extracts affects the distribution of the integumentary pigment (49). Extracts of either subesophageal or of ventral ganglia show a weaker activity. It is uncertain whether the function of the subesophageal ganglion is solely endocrine, or whether a nervous factor is also involved. The potency of corpus cardiacum extracts appears to be greater in some donors than in others. On the other hand, cardiacectomy does not interrupt the mechanisms of color adaptation (49). The corpora allata and the optic lobes whose extracts were tested as controls, were reported to be inert by nearly all investigators (see 146). In some experiments, though not in others, a mild effect was reported for the frontal ganglion. As long as no detailed histological data are available, a correlation between these physiological data and the distribution of neurosecretory cell groups can be attempted only in a general way. Neurosecretion occurs in the brain, subesophageal ganglion, ventral cord, and frontal ganglion of various insects, but not in the optic lobes and corpora allata. The chromatophorotropic effect of cardiacum extracts is accounted for by their content of neurosecretory material. The concept of a storage function of the corpus cardiacum (p. 467) helps to explain the seeming discrepancy between this result and the lack of effects of cardiacectomy on color adaptation. To have validity, the statement that the chromatophorotropin of the brain does not seem to be secreted by the pars intercerebralis (49) lacks support by histological studies. So far, no conclusive evidence speaks against the concept that hormones governing physiological color change originate in neurosecretory cells within the central nervous system.

In addition, insects show morphological color adaptation, such as the variation in body pigmentation in different forms of migratory locusts (81). If nymphs of the gregarious type (orange and black) receive implants of endocrine organs, they may show after the following molt the green pigmentation typical of the solitary type, even when the donor (nymph or imago) belongs to the gregarious type. The source of the hormone involved seems to be the corpus allatum [Joly (80a)] and not the corpus cardiacum as originally stated in the publication (81).

The muscular rhythmicity of the excretory organs (Malpighian tubules) increases up to sixfold in frequency after the administration of brain extracts (90). Further studies regarding a possible "myotropic principle" which is not genus-specific are desirable. There is evidence for the role of a hormone in the initiation of midgut secretion (40). The dimorphism of the prothoracic glands in queen bees and workers suggests a hormonal control of caste differentiation (100; see also 1, 132, 139). In termites, the development of "supplementary reproductives" seems to be suppressed in normal colonies by a substance given off by the king and queen (101, 102).

Invertebrates Other than Crustaceans and Insects

Very little is known about endocrine activities in invertebrates other than arthropods (see 35, 66, 141). In reference to rhythmic movements in isolated

nephridial tubes of sipunculid worms which can be induced or increased in frequency by a substance extractable from these organs, earlier observations were confirmed (89). The substance is present in a variety of organs, resistant to boiling, and acts in very low concentrations. In polychetes, a factor originating in the brain may inhibit the maturation of the gametes (11, 50). The "brain gland" of the centipede *Scolopendra* seems to be a homologue of the lateral frontal organs and thus also of the *x* organs of the crustaceans (44). A hormone (enteramine) present in the gastrointestinal mucosa of ascidians, the posterior salivary glands of cephalopods, and the hypobranchial body of Muricidae increases heart action and oxygen consumption (6, 7, 8, 56). In ascidians, the forerunners of the vertebrates, the functional significance of the neural gland was reinvestigated. The hypothesis advanced to explain the mode of action of the gonadotropin produced by this gland (29) postulates mechanisms whose existence need confirmation. After the injection of mammalian gonadotropin, ascidian ovaries contain corpora lutea which seem to develop by the destruction of almost mature ova and not by the proliferation of granulsoa cells (30). In *Ciona*, ovarian implants prevent the involution of the testis in ovariectomized animals (116).

Physico-chemical Properties of Invertebrate Hormones

Regarding the chemical nature of invertebrate hormones, enteramine (5-hydroxytryptamine) is the only one which has been isolated and synthesized (56). Other invertebrate hormones have been purified to a certain extent (83). Crustacean chromatophorotropins are considered to be substances with a relatively low molecular weight. Some of these crustacean hormones as well as the growth and differentiation hormone and the chromatophorotropin(s) of insects are soluble in water and ethyl alcohol, but not in ether or chloroform; they are resistant to heat and desiccation. The growth and differentiation hormone of lepidopterans seems to be a protein or a smaller molecule bound to a protein (152, 153). It has been tentatively identified in the electrophoretic pattern of "active" insect blood, and it can be biologically assayed by means of tissue culture techniques (84, 153, 155, 185). Invertebrate hormones act in very low concentrations; this also applies to principles produced by neurosecretory cells (49). Differences in the sensitivity of the effector organs determine the kind of hormone response (122, 163).

Biochemical considerations.—Williams and his co-workers (185) postulated that it is the function of the growth and differentiation hormone to obviate a hypothetical chemical deficiency which prevents morphogenesis in dormant pupae. This conclusion was substantiated by a study of the enzyme system in various phases of development. During diapause enzymes of the cytochrome system characteristic of the larva are largely missing, and seem to be replaced by a flavoprotein which functions as a cyanide-insensitive terminal oxidase. From the onset of adult development cytochrome-*c* is formed in increasing amounts; cytochrome-*b*, cytochrome oxidase (and two hydrogenases studied) temporarily decrease before they likewise show a rapid increase. At the same time a marked decrease of flavoprotein is ob-

served. While the flavoprotein system seems to suffice for the metabolism of maintenance, it is not capable of promoting growth and differentiation. The necessity of the cytochrome system, which is similar to that of mammalian tissues (134), for morphogenesis is also demonstrated by the observation, for instance, that development ceases ("artificial diapause") in metamorphosing pupae subjected to carbon monoxide. For other information regarding the interaction of hormones and enzymes, see 32, 79, 91, 108.

Specificity.—As a rule, invertebrate hormones were found not to be specific with respect to genus, order, or sex. This observation was confirmed in recent reports: for the blood sugar hormone and the heart-accelerating factor of crustaceans (69, 151), for the chromatophorotropins of arthropods (49), and for the juvenile hormone (109, 110, 118), the prothoracotropic hormone (77), and the diapause factor of insects (60).

Relationship Between Invertebrate and Vertebrate Endocrines

There are few conclusive cases in which vertebrate and invertebrate hormones were shown to be so closely related that they can replace each other in their action. Many of the reported effects in such hormone exchange experiments are unspecific. This is probably true for the observation of estrogenic activities in invertebrate material such as lobster eggs (47), or insect extracts (159). The alleged presence of epinephrine in the mealworm was shown to be incorrect (64). The growth and differentiation hormone of lepidopterans cannot be replaced by any known vertebrate hormone (152). A well-documented result concerns the similarity between chromatophorotropins of vertebrates and crustaceans which permits the exchange of these substances between members of the two groups of animals (see 28, 72). On the other hand, a recent test with intermedin and epinephrine in insects proved negative (49). A chromatophorotropic principle expanding crustacean (28) and vertebrate pigment (72) is present in the neural gland of ascidians which is believed to correspond to the pituitary. This gland also contains gonadotropin (28, 29) and an oxytocic and vasopressor, but no antidiuretic substance (see 29, 71). An antidiuretic effect was observed in tests with salivary glands of *Octopus*, but the factor responsible for it is said to be different from that of mammals (see 71).

Of particular interest is the observation that crustacean eyestalk extracts which in the crayfish control water metabolism also cause an increase of water uptake in frogs resembling that following the injection of neurohypophyseal extracts. One eyestalk contains approximately the equivalent of 20 milliunits of pitocin (oxytocic fraction of mammalian posterior pituitary). The crustacean principle is unaccompanied by any of the other known posterior lobe activities (71, 72, 73). The analogy observed in this case concerns not only the actions of the hormones, but the organ systems from which they originate. The source of the principle controlling water metabolism and of other hormones in crustaceans is their neurosecretory system (114), in vertebrates the corresponding hypothalamo-hypophyseal

system (9). A third neurosecretory system exists in insects (149); its role in water metabolism has not been definitely established.

The essential features of these three endocrine systems are the production of physiologically active substances by groups of neurosecretory cells within the central nervous system (150), the transport of this material along axons of these cells, and its storage in organs in which the axons terminate. There are strong indications that in insects the corpus cardiacum serves as a reservoir for neurosecretory material produced in the brain (144, 147). This substance is accumulated proximal and depleted distal to the level where the neurosecretory pathway (nervi corporis cardiaci) has been severed (148). The storage concept explains (*a*) why physiological effects demonstrated for the substance present in the corpus cardiacum are the same as those of brain extracts [color change, egg development (170)]; (*b*) why cardiacum implants or extracts are effective, whereas cardiacectomy as a rule has little or no effect (126); and (*c*) why in certain instances brain extirpation does not lead to immediate signs of hormone deficiency. Similarly, certain experimental results in crustaceans (p. 459) which would otherwise be difficult to understand, are adequately explained by the concept that the sinus gland stores hormones produced by neurosecretory cells of the *x* organ and of other parts of the central nervous system. The existence of such neurosecretory mechanisms in two groups of arthropods is of particular interest because, in an analogous situation in vertebrates (hypothalamo-hypophyseal system), neurosecretory material with known physiological properties ("posterior lobe hormones") is stored in the organ (neurohypophysis) where it was formerly believed to originate (9).

The neurosecretory systems are not the only endocrine organs which on comparison in vertebrates and invertebrates have certain features in common (68). The internephridial organs of sipunculid worms closely resemble the interrenal organs of vertebrates [see (141)], the prothoracic glands can be compared with the thymus (143, 168), and the ascidian neural gland [plus ciliated pit (29)] may be considered as an equivalent of the pituitary.

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LIVER[1]

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The liver participates in numerous physiologic processes. Relatively few of these processes are completed wholly by and within the organ. In most instances hepatic activity is but a part of physiologic processes which are initiated, terminated, or both, extrahepatically. It is not feasible to present in a restricted space a review of the data that have accumulated for a period of two years regarding all such hepatic activities. Accordingly, we have attempted to limit the subject material of this review to those researches in which the objectives of the investigation appeared to embrace the liver as an organ, in which hepatic function appeared to predominate and the processes were mainly intrahepatic. In addition, we have attempted to exclude from the review the results of investigations which should more appropriately and authoritatively be reviewed in other *Annual Reviews* such as those of biochemistry and medicine.

New techniques have often proved to be the needed tool for making major discoveries. Several techniques have been presented for the study of various phases of hepatic activity. Brauer *et al.* (1) have developed a method for perfusion of the rat liver which has supplied amazing results. The method is too technical for description in this review. The results obtained with the perfused organ include (*a*) continuous production of bile for periods up to 25 hr., (*b*) an apparent normal histological state up to the terminal phase, (*c*) ability of the reticuloendothelial cells to remove particulate matter from the perfusate, (*d*) excretion of sulfobromophthalein in high concentrations.

Friedman *et al.* (2) describe a method for making a satisfactory biliary drainage in the rat. Essentially it consists in cannulation of the main hepatic duct with a flexible polyethylene tube, which is passed under the skin of the thigh and leg to a point on the dorsal surface of the left foot and thence through the tarsal space to emerge from the foot pad. After the foot has been secured to the bottom of the cage, uninterrupted collection of bile can be made, regardless of movement or position of the animal.

Partial removal of the liver is being increasingly used as a method for making a wide variety of studies of the liver. The operative mortality may be high, especially in case the liver is fatty. Ralli & Dumm (3) have provided an

[1] The survey of the literature pertaining to this review was concluded in June, 1952.

answer to this problem. The important departure in their method from the usual procedure is in the position of the incision, which is made through the skin on the dorsal surface and extends to the left of the spinal column along the edge of the lumbar muscle and the margin of the rib, thus giving access and extrusion of the left lateral and median lobes of the organ.

Abdominal evisceration has been a commonly used method for observing the loss of liver tissue. Drury *et al.* (4) have improved the usual method of removing the viscera by inserting a vinylite tube in the inferior vena cava at the site of the hepatic veins.

The early work on total hepatectomy was performed on geese. A successful operation is difficult. Ranney *et al.* (5) describe a method for functional hepatectomy in the domestic fowl. It consists of tightening two ligatures previously placed around the afferent hepatic blood vessels. Evidence that the circulation of the liver had been almost completely excluded was obtained by lack of penetration into the organ of intravenously injected labeled monosodium acid phosphate and by the rate of removal from the circulation of an intravenously injected insoluble colloidal suspension of P^{32} labeled chromic phosphate.

Cheng (6) describes a technique for total removal of the liver in the rat. It appears to be a two-stage, cellophane band technique adapted to the rat. A one-stage method of hepatectomy in the dog is presented by Nolf & Adant (7). It consists essentially in making a portal-caval fistula and using a vein graft to replace the intrahepatic part of the vena cava removed with the liver. Frank & Jacob (8) remove the liver in one stage by careful and separate dissection of the lobes of liver from the hepatic veins at the point of entrance of the latter into the vena cava and subsequent ligation of the exposed veins. Grindlay & Mann (9) present a two-stage technique for removal of the liver in the dog. At the initial operation the portal vein and inferior vena cava are each partially occluded with a laminated cellophane tape between the liver and the point of entrance of the last tributary. The tape causes a fibrous thickening which partially or completely occludes the vein. Later at a second operation the liver is removed. A midline abdominal incision is used for the first operation and a transthoracic incision for the second operation.

The vascular system of the liver, composed of the arterial and venous components and the lymphatics, is inseparable from the mechanisms of hepatic functions and is an objective of continuous fruitful researches. The recently developed plastic substances for the injection and corrosion techniques have been a valuable addition for investigations of the vascular system of the organ. Employing such a technique, Elias & Petty (10) made a study, too detailed to present here, of the pattern of the major blood vessels in the human liver and a comparison between the vascular system in the human and that of several other species of animals. Holmes & Lovitt (11), using the barium injection technique, studied at necropsy the intrahepatic and major extrahepatic branches of the portal system in normal and cirrhotic livers of the human with special reverence to the alteration in pattern of the latter.

De Ribet (12) has demonstrated fine anastomoses between the right and left branches of the portal vein in the human liver.

Daniel & Prichard (13) studied the passage of contrast media, injected into a tributary of the portal vein, by rapid serial radiography in rats, cats, rabbits, guinea pigs, pigs, and goats. It was noted that the portal blood does not always perfuse the entire liver and sometimes no portal blood could be seen in superficial portions of the organ while the circulation was maintained in deeper areas. No shunts between the portal and hepatic veins were seen. In contrast, Birnie & Grayson (14), on the basis of their method of estimating blood flow by use of thermocouples, concluded that hepatic blood flow shows no great fluctuation with time and varies little in different parts of the organ. They also concluded that the liver is the main site of heat production in the abdominal cavity.

Demling & Kinzlmeier (15) injected acetone-celluloid solutions into the intrahepatic portal vessels when the liver was in a functional state. Corrosion specimens of such preparations showed that the small portal vessels reacted to various substances quite differently from the large branches. For example, epinephrine caused marked constriction of the small vessels without affecting the large ones. Daniel & Prichard (16) stimulated the distal end of the divided hepatic plexus of nerves and noted constriction of the intrahepatic vessels of the portal venous tree in the rat, rabbit, cat, dog, and monkey. This was associated with a marked rise in portal pressure and an acceleration in transhepatic circulation. Intraportal injection of epinephrine caused similar effects but affected mainly the smaller portal vessels. Grayson & Johnson (17), employing a method for compensation of systemic blood pressure, found that epinephrine caused a decrease in intrahepatic portal blood flow. Alexander (18) emphasized the significance of the action of the diaphragm especially in conditions of hyperpnea and shock in compressing the abdominal viscera and thus augmenting the portal blood flow.

Markowitz & Rappaport (19) have written a fine review on the hepatic artery. Researches reported since publication of the above-mentioned review include the following: Grindlay *et al.* (20) corroborated the work of Markowitz regarding the beneficial effects of administration of antibiotics after occlusion of the arterial blood supply to the liver and, by means of barium injections, studied the development of the collateral circulation after ligation; Burnett *et al.* (21) described the regional anatomy with particular reference to the hepatic blood vessels and concluded from results of ligation experiments that arterial blood was not essential for normal liver cell function in the rat; Raffucci & Wangensteen (22) found that 20 min. was the maximum period of continuous occlusion of hepatic artery and portal vein tolerated by the normal dog without showing evidence of necrosis; Karn & Vars (23) noted that restoration of the liver was not impaired by ligation of the hepatic artery in the rat; it was surprising to learn that sudden and complete occlusion of the portal vein in the *Macaca mulatta* monkey did not cause death [Child *et al.* (24)] and that in this species acute occlusion of the portal vein or hepatic

artery had small effect on function of the liver or hepatic morphology [Child *et al.* (25)]; ligation of the hepatic artery of man has been done for treatment of cirrhosis with as yet unconclusive results [Berman *et al.* (26); Rienhoff (27); Egbert & Raber (28)].

Using various injection techniques, Johnson & Mann (29) made a comprehensive study of the intrahepatic lymphatic system in several species of animals. Microscopic examination revealed an intimate association existing between the lymphatics and all the other important anatomic components of the organs. Of special significance were the relationship of the lymphatics to the biliary system and the generous lymphatic distribution within the walls of the bile ducts.

Anatomically and physiologically, hepatic tissue is very suitable for studies on growth. Siess & Stegmann (30) investigated the growth of the liver in the mouse as a basis for morphologic and functional studies. They found that throughout the period of growth the weight of the liver remains a relatively constant fraction of the body weight. Growth by multiplication ceases at birth, although it remains demonstrable for the first week. Growth then corresponds to the increase in volume of the liver cells but the relation of the size of the nucleus to that of the cell remains constant. A protein diet increases the weight of the liver slightly. Flexner & Flexner (31) noted that growth of the liver of the fetal guinea pig is accompanied by an increase in intracellular water and a decrease of extracellular water per unit weight of tissue. The concentrations of cellular water and protein remain practically constant throughout the period of gestation.

The storage capacity of the reticuloendothelial cells of the liver was determined by Toro & Velossy (32) by the use of colloidal silver, copper, and iron. They found that the injection of one colloidal substance decreased the uptake of a second colloidal substance if the period of time between injections was short. The iron content of the liver was found to increase steadily for the first two weeks after whole body exposure to x-rays and then decrease during the third week after irradiation [Ludewig & Chanutin (33)]. Shore & Zilversmit (34) measured the disappearance of P^{32} labeled plasma phospholipids from the plasma and sulfobromophthalein retention in dogs before and after injection of India ink. There was a marked increase in the retention of the dye but no alteration of the turnover time of the plasma phospholipids after administration of the ink. Pigment granules of a melanin nature were observed to appear in the stellate cells following adrenalectomy [Müller (35)].

The liver is an important factor in the mechanism of shock of various types. Nothacker & Brauer (36) found that long-continued infusion of histamine at subshock rates produced a definite hepatic lesion. From results of observation on Eck fistula dogs, it was concluded that intestinal congestion and hemorrhage in the posttransfusion phase of irreversible hemorrhagic shock was due to intrahepatic obstruction to portal outflow [Frank *et al.*(37)]. Wayne *et al.* (38) performed cross-circulation experiments with dogs in which hypotension was produced by bleeding, the hypotensive animal re-

ceiving blood by way of the splenic vein. They found that such animals survived longer than if blood was given in systemic vein. From their results they concluded that an adequate hepatic circulation greatly increased the period of arterial hypotension necessary to induce irreversible shock. Ferritin was found to be ineffectual in altering the survival period of hepatectomized-nephrectomized dogs in hemorrhagic shock [Frank *et al.* (39)]. The intravenous injection of trypan blue was reported to produce shock in dogs similar to anaphylaxis with fall in arterial pressure. The complete exclusion of the liver from the circulation prevented this reaction, but it will occur if the dye is permitted to reach the liver only through a restricted hepatic artery [Czarnecki *et al.* (40)].

Even though the secreting function was the first hepatic activity to be recognized, it maintains a considerable amount of current interest to investigators. The values of the secretory pressure, rate of flow, specific gravity, pH, daily excretion of cholesterol, and bilirubin of the bile in the rat were found to differ very little from data obtained on other species of animals under similar experimental conditions [Friedman *et al.* (2)]. It was noted in studies on acute biliary fistula dogs and rats that the basal rate of bile flow did not correlate with either the surface area or body weights in the dog, but there was a significant correlation with both in the rat [Cook *et al.* (41)]. Gallbladder bile contained less phosphatase than fistula bile in the dog. The daily output of phosphatase in fistula bile was variable but was at least 26 units per kilogram per hour [Dalgaard (42)]. Studies on bile fistula rats indicated that there is little intestinal absorption of urobilinogen, a conclusion based on the findings that the parenteral administration of crystalline urobilinogen was followed by the prompt excretion of about 75 per cent of the injected amount in the bile, whereas, when the urobilinogen was given orally, very little was recovered in the bile [Mann & Koler (43)]. The rates of appearance in the bile and disappearance from the blood serum of labeled phosphorus were determined in rabbits with acute biliary fistula. Bile from the common duct reached a maximum activity between 0 and 15 min. after injection and contained less activity than the blood serum at the same time. The rate of decrease in the bile from the maximum value paralleled that of the serum. The activity of the latter was 5 to 24 times that of the bile. Bile from the gallbladder was intermediate in activity between the bile from the common duct at the maximum and at the end of 2 hr. [Moreland & Halpert (44)]. The excretion of selenium in the bile of a bile fistula dog after intraperitoneal injection of sodium selenate containing radioselenium was initially rapid followed by a prolonged slower rate with a maximum excretion in 48 hr. of a total amount of 2.56 per cent of the amount administered. The biliary selenium was, to a considerable amount, nondialyzable, indicating that it was in organic combination. There was some evidence that selenium was in combination with bilirubin [McConnell & Martin (45)]. The results of studies on bile fistula dogs indicated that an intact flow of bile from the liver to the intestine is not essential for the production of diuresis by organic mercurial

diuretic [Pratt *et al.* (46)]. Bile collected from rats in which fatty livers had been produced by a diet low in choline was found to be less in amount and to contain less bile lipid than bile from normal rats [Colwell (47)]. Ox bile extract, sodium glycocholate, and taurocholate were found to be effective in decreasing the amount of fecal fat in bile fistula dogs [Searle & Annegers (48)]. Partial removal of the liver decreased total bile volume output for a considerably longer period than it decreased the output of some of the biliary constituents such as cholic acid and cholesterol [Fisher *et al.* (49)].

Additional work on the mechanism and significance of the direct and indirect reactions of bilirubin has been presented. Najjar & Childs (50) describe two different crystalline forms of bilirubin. Bilirubin prepared from indirect reacting serum crystallizes rapidly as long, thin neeedles, while that from direct reacting serum forms slowly as short, blunt rods. On the other hand, Klatskin & Drill (51) have presented evidence that the characteristic difference which exists in the rate of diazotization of bilirubin depends, not on the existence of two different forms of bilirubin, but on several factors including the concentration of pigment and other substances in the serum. With (52) summarizes the evidence against the theory that the direct reaction is due to the bilirubin having passed through the liver cell. Barac (53) reports that biliverdin, like bilirubin, forms a nonultrafiltrable complex with serum albumin.

Kim *et al.* (54) investigated various factors that might influence the output of bile acids in biliary fistula dogs. They found that supplements of amino acid solution containing the 10 essential amino acids with glycine evoked a highly significant increase in the daily output of cholate. Vitamin B_{12} increased the cholate output for the first 24 hr. only. Reiners (55) corroborated previous work concerning the rapid increase of bile acids in the thoracic duct lymph, and then concentration in the blood following obstruction to the biliary outflow. Friedman *et al.* (56) determined the plasma bile acids in normal rats and in animals with ligated bile ducts and obtained evidence which suggested that the liver continues to discharge bile acids into the blood after biliary obstruction.

Cholesterol has remained as the most enigmatic of the main known constituents of bile. Knowledge concerning its origin, physiologic significance, and fate is incomplete. Accordingly, the recent investigations on the substance are timely. The cholesterol of rat bile was found to be mainly in the free form and the total biliary excretion varied greatly [Friedman *et al.* (2)]. Obstruction of the biliary outflow was followed by a rapid and marked rise in the free cholesterol content of the plasma with a much slower and lesser rise in esterified cholesterol. The injection of free cholesterol into biliary obstructed rats accelerated the increase of free cholesterol in the plasma but did not affect the rate of increase attributable to obstruction [Byers *et al.* (57)]. After partial removal of the liver, obstruction of the biliary outflow was not followed by the increase in content of plasma cholesterol [Byers *et al.* (58)]. Restoration of the plasma cholesterol content after reduction by

plasmapheresis was delayed for 24 hr. by partial removal of the liver [Friedman *et al.* (59)]. The hypercholesteremia after biliary obstruction appeared to be due to the retention of some substance from which cholesterol was formed [Byers & Friedman (60)]. Experimental hypercholesteremia was produced by the intravenous injection of sodium cholate into normal fasting rats [Friedman & Byers (61)]. However, Kellner *et al.* (62) produced hyperlipemia with hypercholesteremia by intravenous injection of surface-active agents unrelated to cholesterol. Obstruction of the biliary outflow was followed after 72 hr. by a fivefold increase in the bile acid content of plasma over the normal value [Friedman & Byers (63)]. Cholic acid, fed to the bile duct obstructed rat, markedly increased the hypercholesteremia associated with such obstruction [Byers & Friedman (64)]. A reduction in liver function by surgical (hepatectomy), chemical (carbon tetrachloride administration), and metabolic (thiouracil administration) means greatly reduced the biliary excretion of cholesterol, while hepatic stimulation (powdered thyroid administration) markedly increased excretion of cholesterol in the bile [Byers & Friedman (65)]. The amount of cholesterol secreted in the bile of bile fistula rats with fatty liver produced by feeding a diet low in choline is less than the amount found in the bile of normal rats [Colwell (47)]. The ingestion of cholesterol by Eck fistula dogs decreased the rose bengal dye clearance, increased the plasma and liver cholesterol content and the liver fat, and decreased the phospholipids as compared with normal dogs, thus indicating a decreased ability to catabolize cholesterol and synthesize phospholipids [Bailey (66)].

The fact that the liver excretes certain dyes has proved to be one of the most valuable hepatic activities from the standpoint of clinical diagnosis of hepatic disease. The more recent use of sulfobromophthalein for the estimation of hepatic blood flow in addition to estimating hepatic function makes fundamental studies on the excretion of the dye increasingly valuable. The clearance and maximum excretory capacity for sulfobromophthalein was determined for rabbits by Lewis (67), and for dogs both normal and those with bile fistula, and with liver injury by Brauer & Pessotti (68). A constant infusion technique was used which made possible the measurement of the rate of dye removal from the blood stream per unit of time. It appeared that, below saturation level, hepatic clearance is independent of plasma concentration and varies with the hepatic blood flow in the rabbit. In the normal dog, the calculated hepatic sulfobromophthalein uptake represents 77 to 89 per cent of the amount injected. Dog livers injured with carbon tetrachloride had decreased capacity to remove the dye. Baker *et al.* (69) found that when sulfobromophthalein and sodium cholate were injected together, the concentration of the dye in the serum was abnormally elevated shortly after injection while the cholate concentration remained normal. After hepatic injury with carbon tetrachloride, the dye excretion was definitely delayed with little change in cholate excretion. Wirts *et al.* (70) reported that, in bile fistula dogs with livers injured by prolonged administration of carbon tetra-

chloride, decreased excretion of sulfobromophthalein was not accompanied by a significant or consistent decrease in bile volume or output of endogenous pigment until very low functional levels were reached. Lorber & Shay (71) studied the intestinal absorption of sulfobromophthalein in the human and found that with large doses there was an enterohepatic circulation of small amounts of the dye. Owen (72) introduced sulfobromophthalein in large doses directly into the stomach of humans and could not detect the dye in the blood. Cohen *et al.* (73) found that excretion of sulfobromophthalein was not affected by a simultaneous administration of galactose in the human. Zieve *et al.* (74) similarly found it to be unaffected by simultaneous galactose tolerance and hippuric acid tests. Giges *et al.* (75) reported that, in dogs and rats with complete biliary obstruction, the retention of sulfobromophthalein was of much shorter duration than that previously observed in man.

Although three quarters of a century has passed since the Eck fistula was first described, it continues to be a method for studying the liver. Eck fistula formation was found to be followed by the following changes in the alloxan diabetic dog: (*a*) an increased insulin requirement to prevent glycosuria, (*b*) usually an increase in the nonprotein nitrogen and sugar excretion in the urine, (*c*) altered excretion of individual amino acids during periods of uncontrolled diabetes, and (*d*) a reduction in lipemia [Koide & Freeman (76)]. Rappaport & Lotto (77) employed the Eck fistula with a subsequent occlusion of the hepatic artery to produce ischemia of the liver which resulted in coma not unlike the condition seen in the human.

Several recent reports of researches on the eviscerated animal have been made. While it is recognized that the results obtained by this method of investigation are complicated by many factors, especially by the loss of tissues and function other than hepatic, we are citing some of these investigations because the conclusions, by the importance of their implications relative to liver function, appeared pertinent to the subject of the review. Eviscerated rats given continuous injections of glucose supplemented with insulin have supplied the following data: a progressive increase in the prothrombin time and failure of the blood to clot which was not affected by the administration of vitamin K [Ingle *et al.* [78)]; no significant change in concentration of hemoglobin or red cells; in serum inorganic phosphorus or plasma sodium; a decrease in white cells, in plasma proteins and serum calcium; the development of an acidosis and jaundice [Ingle *et al.* (79)]. Eviscerated fasted rabbits injected with C^{14}-labeled glucose eliminated only a small portion of carbon dioxide originating from the tagged glucose [Drury *et al.* (80)]. Using a preparation and procedure similar to that of the above-mentioned research, it was found that insulin acting on the extrahepatic tissues greatly increased their combustion of glucose to carbon dioxide [Wick *et al.* (81)]. The oxidation of intravenously injected methionine S^{35} to sulphate occurred readily in the nephrectomized dog but not in the eviscerated dog, suggesting that the process occurred in the liver [Forker *et al.* (82)]. No evidence was found for the

utilization of galactose in eviscerated nephrectomized dogs and rats [Levine *et al.* (83)].

Restoration of hepatic tissue after partial removal or injury is one of the outstanding characteristics of the liver. Researches on the various physiologic factors involved in the process of hepatic tissue restoration are important, not only for elucidation of the process itself but also because the newly formed liver tissue has proved to be valuable for studies of intracellular processes.

Grindlay & Bollman (84) removed approximately 70 per cent of the liver of normal dogs and of dogs in which the hepatic venous circulation had been shunted or restricted in various ways. They noted (*a*) rapid restoration in normal dogs, (*b*) complete restoration after portal-caval anastomosis and ligation of the vena cava cephalic to the stoma, (*c*) only slight restoration following an Eck fistula, (*d*) almost normal restoration following ligation of the vena cava with portal-caval anastomosis and ligation of the portal vein, and (*e*) only slight restoration after previous occlusion of portal vein. The simultaneous ligation of the portal vein and cutaneous abdominal vein was followed by less hepatic regeneration after removal of approximately 60 per cent of liver mass in the toad [Flores (85)]. Bucher & Glinos (86) found that young rats had far greater ability to restore liver mass and form new cells after partial hepatectomy than did adult or old rats.

Aterman (87) made an extensive cytological study of the liver tissue of normal and partially hepatectomized rats fasted for various periods. He noted several interesting alterations in the cytology of the liver tissue some of which might occur within 5 min. after removal of 70 per cent of the organ. Among these alterations was the development within the hepatic cell of glycogen-free, fat-free vacuoles which he considered identical with anoxic vacuolation. The vacuoles did not occur in animals that had been fasted for 48 hr. before operation. Harkness (88) found that 24 hr. after partial hepatectomy in the rat the cells in mitosis were mainly periportal in distribution. This distribution was no longer seen at 48 hr. after operation.

The increase in total fats and fatty acids noted in the first few days in the regenerating liver after partial removal is greatly reduced by splenectomy, although the restoration of the hepatic tissue proceeds in a normal manner [Pontremoli & Arrigo (89)]. Forced exercise did not alter the restoration of the liver after 70 per cent removal in rats [Mellinkoff & Machella (90)]. When one rat of a parabiotic pair was partially hepatectomized the unoperated liver of its partner increased in net weight and in number of hepatic cells. These findings were attributed to a growth stimulus carried in the blood from the operated to the unoperated animal [Wenneker & Sussman (91)]. Moderate amounts of fat in the diet of rats were not deleterious for liver restoration after partial removal [Rogers *et al.* (92)]. Vitamin B_{12} appeared to enhance the rate of restoration after partial hepatectomy in the rat [Dumm & Ralli (93)]. The rate of liver regeneration in partially hepatectomized rats was signifi-

cantly accelerated by the addition to the diet of ribonucleic or desoxyribonucleic acid, or of tissues rich in nucleic acids [Newman & Grossman (94)].

The renal clearance of sulfonamide and inulin in partially hepatectomized rabbits was impaired in proportion to the extent of liver removed. The renal function improved as the liver tissue was restored [Zoboli *et al.* (95)]. Removal of the adrenal glands impaired the deposition of protein in the liver following partial hepatectomy, and adrenal cortical extract restored the liver's regenerative power to form new tissue proteins [Friedgood *et al.* (96)]. Irradiated ergosterol appears to hasten regeneration of the liver [Capocaccia & Ardy (97)]. Splenectomized, partially hepatectomized rats had a decreased respiratory quotient during the first two days after operation as compared with animals with only partial hepatectomy [Pontremoli & Montini (98)]. Acetylation of sulfanilamide was not noticeably influenced by partial hepatectomy [Zoboli *et al.* (99)].

Several reports indicate a relationship between hepatic restoration and the formation of neoplasms. Glinos *et al.* (100) found that butter yellow produced tumors in the regenerating livers of rats following partial hepatectomy more rapidly than in control animals but did not alter the final total tumor mass. Buckley *et al.* (101) observed that butter yellow induced tumors more slowly in rats with fatty liver resulting from choline deficiency than in control animals fed choline supplements.

Complete removal of the liver continues to be a successful method for determining the relative significance of hepatic activity in various physiologic processes. In dehepatized dogs the rate of disappearance of intravenously injected glucose from the blood was found to be slower in the first hour than in the second hour, suggesting that the injected glucose stimulated the secretion of insulin which accelerated the rate of removal of sugar from the blood by extrahepatic tissue [Mackler *et al.* (102)]. The development of new techniques for quantitation has made possible more detailed study of certain effects caused by loss of liver tissue. It was found by microbiologic technique that there was a quantitative difference in the response of individual amino acids of plasma in the dehepatized dog. One group (glycine, glutamic acid, histidine, and lysine) consistently showed an increase within 12 hr. after removal of the liver. A second group (arginine, leucine, methionine, tryptophan, and valine) decreased. A third group of seven amino acids showed no consistent change [Freeman & Svec (103)]. Somewhat different results in respect to certain amino acids were obtained by paper chromatography. The characteristic chromatogram of the amino acids of the plasma of the normal dog was maintained after hepatectomy, but each spot was intensified, indicating an increase in concentration. All 15 amino acids or derivatives were found to increase [Flock *et al.* (104)]. Conjugation of amino acids occurs after liver removal and a large portion of the amino acids excreted in the urine is in the conjugated form [Flock *et al.* (105)]. The rate of increase of the amino acid content of plasma of the dehepatized dog was greater when no or mini-

mal amounts of glucose were given than when larger amounts were injected. A large increase in concentration of free amino acids of the brain was noted after total removal of the liver. To a considerable extent the increase was of glutamine and the rate of increase was progressive and not related to the glucose concentration of the blood [Flock *et al.* (106)]. There appears to be a parallelism in the increase of glutamine and ammonia in the dehepatized dog [Gordon *et al.* (107)]. The loss of liver tissue frequently greatly alters the action of a given substance. Usually the action of the specific substance is enhanced, as in the case of 2,4-dinitrophenol, the intravenous administration of which causes a much more marked rise in rectal temperature of the dehepatized animal than in a normal animal, although the blood sugar is increased in the latter but maintains its progressive decrease in the former [Ryan (108)]. Rarely, complete hepatectomy reduces the specific action of some substances, as the vasopressor action of epinephrine [Page (109)]. It was found that after removal of the liver the disappearance of T1824 was within normal limits for normal animals, sulfobromophthalein disappeared from the blood, and cardiac output was reduced [Werner & Horvath (110)]. In the toad, bleaching of the visual purple was found to be retarded after hepatectomy but not by splenectomy, nephrectomy, or pneumonectomy [Peng (111)].

The development of new techniques for cannulating the liver lymphatics, which in turn was dependent on development of suitable tubing, has made possible the securing of specimens of hepatic lymph worthy of detailed analysis. The more important findings to date are: the concentration of phospholipids, cholesterol, and total fatty acids was found to be similar to that of plasma and did not change appreciably during absorption of fat from the intestine [Bollman *et al.* (112)]. In anesthetized dogs the volume of hepatic lymph was equivalent in 24 hr. to 47 per cent of the estimated plasma volume. In dogs with experimentally produced hepatovenous congestion and in dogs with cirrhotic livers the flow of hepatic lymph was two to five times that found in normal animals; the equivalent of 70 to 200 per cent of the total circulating plasma proteins passed through the hepatic lymphatics of animals in 24 hr. [Nix *et al.* (113)]. The concentration of cholesterol in liver lymph was not altered by cholesterol feeding in rats. In animals with experimental liver injury, the liver lymph contained relatively more free cholesterol than the thoracic or intestinal lymph. After feeding free cholesterol to such animals, the intestinal lymph contained increased amounts of esterified cholesterol similar to that obtained from normal animals [Bollman & Flock (114)]. Hepatic lymph, in contrast to intestinal lymph, was found to contain very few lymphocytes [Mann & Higgins (115)].

In dogs the concentrations of protein and amylase in liver lymph approximated those in the blood serum. In experimental peritonitis bacteria identical with those found in the peritoneal cavity appeared in the liver lymph within 3 to 18 hr. after production of infection. After intramuscular

injection of penicillin, the concentrations of the substance were nearly the same as those in the blood [Gardner *et al.* (116)].

Some current researches have added further data regarding hepatic activity in relation to the process of coagulation of the blood. Nolf & Adant (117) studied changes in coagulation after hepatectomy using preparations in which the vascular anastomoses were made with transplanted segments of vein, with paraffin coated glass tubes or with uncoated glass tubes. In all instances fibrinogen, thrombogen, and antifibrinolysin decreased; these changes were most rapid in the preparations employing uncoated glass tubes. Mann *et al.* (118) observed that prothrombin, cothromboplastin, the labile factor, and fibrinogen all decreased rapidly after hepatectomy; cothromboplastin uniformly more rapidly than prothrombin. Solvonuk *et al.* (119) administered vitamin K (menadione) labeled with C^{14} to vitamin K-deficient dogs and found no localization of the vitamin in the liver. This finding, which contradicts the widely held belief that vitamin K goes to the liver, is strengthened by the fact that definite localization of bishydroxycoumarin (Dicumarol) in the liver was demonstrated in the same laboratory with similar techniques [Lee *et al.* (120)]. Binet *et al.* (121) extracted from dog liver a lipid anticoagulant different from heparin. From the method of preparation it would appear similar to lipid anticoagulants prepared from various tissues by Tocantins, Overman, Flynn, and their collaborators [reviewed by Flynn & Coon (122)]. It may even be speculated that the heparin of Howell and McLean, first described as a lipid, might have been Tocantins' inhibitor rather than the well-known crystalline carbohydrate which now bears the name.

Some of the researches on enzymes are mentioned in this review because they appeared to be within the scope of our objectives. Freeman (123) made a comparison of the effects of complete hepatectomy and common bile duct obstruction on the serum alkaline phosphatase of adult dogs. The much more marked increase in serum phosphatase following common bile duct obstruction as compared to total removal of the liver was considered unequivocal evidence that the increase in the serum phosphatase following obstruction to biliary outflow is largely hepatic in origin rather than extrahepatic. The diet prior to obstruction influences the rate of rise in serum phosphatase following obstruction of the common bile duct. The results of the experiments of Flock *et al.* (124) on the effect of removal of the liver on serum alkaline phosphatase are in accord with those of Freeman. Talageri *et al.* (125) concluded from the results of experiments in which the liver of rats was injured by carbon tetrachloride that the role of the liver in phosphatase metabolism is primarily that of a regulatory organ concerned with the excretion of surplus phosphatase.

Miller (126) found that maintenance of rats on low or nonprotein diets is associated with the loss of liver protein and liver alkaline phosphatase activity. Refeeding a high protein diet leads to prompt restoration of both liver

protein and enzyme activities. He considers these results to support the theory that hepatic enzymes, as proteins, participate in a dynamic nonspecific manner in the metabolism of proteins in general. Rosenthal *et al.* (127) recognized two types of hepatic alkaline phosphatase which are affected slightly differently by protein depletion and partial hepatectomy. In their experiments protein starvation was associated with an increase of the alkaline phosphatase content of the liver by 28 per cent while the hepatic protein decreased 43 per cent [Rosenthal *et al.* (128)].

Norberg (129) noted that following partial removal of the liver phosphatase was produced at the same rate as the rat liver tissue was restored. LeVeen *et al.* (130) found that intravenously injected alkaline phosphatase in dogs was rapidly removed from the circulation and secreted in the bile in amounts equal to those injected. Dalgaard (131) reported that transfusion of phosphatase-rich blood from dogs with obstructive jaundice into normal dogs produced approximately the increased value of phosphatase in the recipients that would be expected if the enzyme was distributed only in the serum of the recipient.

Harrison & Brown (132) made the interesting observation that the concentration of cholinesterase of liver and serum of the male rat was unaltered by fasting while in fasted female rats it fell rapidly in both liver and serum. No change in serum cholinesterase was noted during 20 hr. of survival after total removal of the liver [Jacob *et al.* (133)]. The normal range of cholinesterase appears to vary widely in the normal human being [Mann *et al.* (134)].

Investigations on other enzymes in relation to liver function indicated that liver catalase activity gradually increased after partial hepatectomy [Stein *et al.* (135)]. It was shown that after partial hepatectomy the regeneration of arginase was stimulated by increases in the protein catabolism of the rat whereas the restoration of adenosinepyrophosphatase and rhodanase was independent of the nutritional state [Rosenthal *et al.* (136)]. No significant alteration in amylase activity of the plasma was noted after total removal of the liver [Flock *et al.* (124)].

In keeping with the current major interest, there have been recent investigations of the effect of irradiation on the liver. It was found that a single massive dose of roentgen rays produced injury involving all the component parts of the liver [Ariel (137)], that whole body irradiation was followed by a marked increase in liver size [Supplee & Entenman (138)], and that sublethal irradiation caused a decrease in glucose tolerance and hepatic glycogen formation [Lourau & Lartigue (139)] but did not affect alkaline phosphatase activity [Ludewig & Chanutin (140)]. Ultrasonic irradiation for 40 min. caused complete loss of glycogen from the cells of freshly excised hepatic tissue [Bejdl (141)].

One of the oldest theories concerning liver function, based on the anatomic fact that the portal blood, containing substances absorbed from the intestinal tract, passes through the liver before mixing with the systemic blood, is that

the liver filters out toxic substances present in the portal blood, destroying or inactivating them more efficiently in one passage through the organ in high concentration than when these substances reach the organ in a lower concentration after being diluted with systemic blood. This theory has received only meager support except in regard to the engulfing of particulate substances by the stellate cells. However, the theory has been used extensively in investigations which attempt to prove that the liver inactivates various hormones. The results of recent studies are inconclusive in this regard. Complete inactivation of ovarian secretions affecting growth and uterine size was not obtained after intrasplenic ovarian transplantation in immature ovariectomized rats [Werthessen & Field (142)]. Adrenal cortical activity, according to tests involving life maintenance, growth, and the deposition of glycogen in the liver, was the same in adrenalectomized rats with viable transplants of adrenal cortex in the spleen as in the controls [Read (143)]. The alloxan hypoglycemia of adrenalectomized rats did not occur in animals with intrasplenic transplants [Bernstein & Enoch (144)]. Thyroxine is more effective when given subcutaneously than intraperitoneally following obstruction of the biliary outflow and partial hepatectomy [Grad & Leblond (145)].

While it has been possible to study hepatic blood flow in animals by several methods, estimation of the blood flow to the liver of man is restricted to clearance techniques, which in turn have been made possible by blood vessel catheterization. Current reports on the clearance technique for estimation of the hepatic blood flow would appear to indicate that the method is still in a developmental phase. Sherlock *et al.* (146) concluded that, when hepatic blood flow is estimated in man by the sulfobromophthalein method, extrahepatic removal of the dye causes spuriously high value when the sulfobromophthalein level is less than 1 mg. per 100 cc. Myers (147) reports disagreement with the preceding statement. In this connection it should be noted that Werner & Horvath (148), employing a similar technique in anesthetized dogs, obtained results in marked contrast to those obtained in man by Sherlock *et al.* (146). The former investigators corroborated the data of Brauer & Pessotti (68) regarding the extrahepatic removal of approximately 20 per cent of the sulfobromophthalein extrahepatically. After their data obtained by the sulfobromophthalein method had been corrected for this 20 per cent loss of dye from the peripheral blood, values for hepatic blood flow were in close agreement with those obtained by other methods. They concluded that hepatic blood flow is subject to wide spontaneous variations and a single observation represents only the blood flow under conditions during that period of observation.

There is a considerable amount of current research relating to dietary factors that are involved in the processes which control fat deposition in the liver, protect the liver from injury, and are associated with the development of massive hepatic necrosis and cirrhosis. Restriction of space prevents their review in this article. Special mention should be made of the review by Best

et al. (149) on protection of the liver by dietary factors, of that by Drill (150) on hepatotoxic agents regarding their mechanism of action and dietary relationships, and of papers with discussions presented at the Ninth (151) and Tenth (152) Conferences on Liver Injury of the Josiah Macy Jr. Foundation. These latter publications also contain important articles on other subjects that cannot be reviewed here, such as liver biopsy. An extensive review of the rapidly increasing literature on hepatic function tests was written by Popper & Schaffner (153). Snavely (154) has reviewed the work dealing with hepatic factors in salt and water metabolism. The Ciba Foundation Symposium on Liver Disease (155) also contains material concerned with hepatic physiology.

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HIGHER FUNCTIONS OF THE NERVOUS SYSTEM[1,2]

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The period since 1949, when the topic of "Physiological Psychology" was last surveyed for the *Annual Review of Physiology*, has been particularly productive. Because it is not possible to survey effectively all the areas of physiological psychology covered during that time or even during the last year, the very important topic of the cortical localization of intellectual functions has been selected for review. A series of major researches and truly noteworthy contributions has been effected in this area during the last three-year period. Five important books dealing in whole or in part with this research field have appeared since the 1949 *Review* (12, 21, 24, 33, 38).

The Cerebral Cortex of Man (38) summarizes results of studies on the human brain conducted at McGill University over a period of almost two decades. Many of these studies involve electrical stimulation of the cortex of the conscious patient, with records supplemented by electrocorticograms and electroencephalograms. The effects of cortical lesions ranging from small excisions to bilateral lobectomies are also reported. Much of the material of the book is concerned with somatomotor responses, eye movements, and visceral responses, and, as such, is beyond the scope of the topic being reviewed. Chapter V describes electrical stimulation studies which outline two areas, one in the inferior portion of the precentral gyrus, and the other in the superior intermediate frontal area, which when stimulated might give rise to spontaneous vocalization or to word arrest if the patient is talking. Three areas of aphasic arrest, one in the frontal, one in the parietal, and one in the temporal lobe of the dominant hemisphere, are also identified. Stimulation of these areas produces temporary word confusion and substitution similar to symptoms found in patients suffering from aphasia.

Stimulation of the temporal (probably extending into the occipital) cortex may produce visual or auditory illusions or both, hallucinations, dreams, and memories. Though the visual phenomena are usually elicited by stimulation more distant from the lateral fissure than are the auditory phenomena, visual phenomena may be elicited from stimulation over an extensive area of the temporal lobe. These phenomena take on added interest in view of the findings from both the Wisconsin and the Yerkes laboratories that temporal lobe lesions may seriously affect the learning of visual discriminations and other visually guided problems by rhesus monkeys. Although Penfield and associates emphasize the role of the temporal lobe in relation to memory, there is evidence to indicate that the neotemporal cortex serves

[1] The survey of the literature cited was completed in July 1, 1952.

[2] The following abbreviations are used in this chapter: PTO (parieto-temporo-occipital); CFF(critical flicker fusion).

a more comprehensive role in the mediation of visual and auditory learned responses.

The effects of both bilateral frontal lobectomies and gyrectomies are also described. The case of K. M. (who showed few or no symptoms) has been described in detail by Hebb (21) and now constitutes a *cause célebrè*. The reported frontal gyrectomies are described as having had relatively little effect upon mental or physical state, although Malmo (31), on the basis of somewhat fragmentary testing, had previously described more severe loss for these cases than is implied in this book and, also, more severe loss than that reported for subjects in the Columbia-Greystone project.

Cerebral Mechanisms in Behavior: The Hixon Symposium (24) is a collection of six essays bearing some relation to cortical function. At the end of each paper a panel of discussants almost invariably presents an uncritical appraisal of the paper; indeed, the discussants typically seem far more eager to memorialize some personal observation or incomplete experiment of their own than to enter into any critical discussion of the problems of cortical function. The first essay, by J. von Neumann, shows that there are analogies between computing machines and living organisms, and W. S. McCulloch, in the second paper, subsequently assures us that the brain is a mechanism complicated enough to account for human behavior. K. S. Lashley's paper presents a scholarly and critical analysis of the theoretical problems involved in the spatial and temporal serialization of the neurological mechanisms concerned with the orderly arrangement of action and thought. H. Klüver and W. C. Halstead present, with some simplification, materials already extant in monograph form, and detailed references to these chapters are made in a subsequent section of this review chapter. W. Köhler, in the sixth paper, summarizes the status of his experiments designed to show that the processes underlying object vision are direct currents measurable by changes in the occipital surface potential. The merit of the book (24) lies in its coverage of a wide range of materials related in some way to cortical functions. The shortcomings of the book are the lack of integration between the separate chapters and the failure of the discussants in most cases to appraise the contributors' work critically, to evaluate properly the present status of cortical psychophysiology, and to outline needed areas of future research.

Selective Partial Ablation of the Frontal Cortex (33) represents a collaborative venture by more than fifty investigators who conducted medical, physiological, sociological, and psychological studies on 48 psychotic patients: 24 controls and 24 subjected to brain surgery, usually involving the bilateral removal in the frontal lobe of one or more of the cytotechtonic areas described by K. Brodmann. Although reference is subsequently made to specific portions of this book, we refer here only to a paper by Landis, Zubin & Mettler (26), which summarizes the psychological findings, relates them to other researches, and presents an integrated theory of human frontal lobe functions.

Although no evidence of permanent intellectual change was demon-

strated in the operated patients on any psychological test or group of tests, Landis and co-workers stress the fact that the operations nevertheless produced psychological changes. Real and marked changes occurred immediately after operation, but these changes were variegated and transient, differing in degree and kind from patient to patient and from test to test. An interpretation is made, in terms of Head's (20) theory of vigilance, by Landis *et al.*

> These transient alterations following psychosurgery may be attributed to a decreased vigilance of the nervous system whose efficiency or capacity is lowered by the immediate effects of the surgery and their physical sequelae (26, p. 131).

Two more permanent psychological changes—decrease in anguish and motivational loss—are reported. The decrease in anguish was demonstrated both by observation and by formal tests. "During a half year after operation there is clear verbal and behavioral evidence that the anguish or morbid emotion has evaporated or is diminished in a half to a third of those operated" (26). The report of motivational loss is based on clinical observations by others and themselves, not on systematic experimental study. The authors state:

> The diminished zeal shows itself in a variety of small ways in psychological examination as well as in everyday life. It takes more urging to get such a patient to give his best performance six months or a year after operation. He can do the tests, but usually he has to have an occasional prodding remark by the examiner to keep him going. In family life it is often reported that the recovered patient is lazy and careless (26).

Not only do Landis and associates make it clear that they believe that psychosurgery on the frontal lobes (lobectomy, topectomy, lobotomy) produces psychological changes, but they suggest two hypotheses to account for these alterations:

> . . . psychosurgery decreases in an unspecific fashion, either peripheral attention, or the particular phenomenological attribute of feeling of familiarity. If the patient loses his psychic pain or psychosis, he may remark that the voices, the ideas are somehow detached from him. They can now be neglected, although if he thinks about them they are still available. The patient with intractable pain likewise becomes less bound to or familiar with his pain following operation (26).

In his book, *The Organization of Behavior*, Hebb (21) has attempted the difficult task of formulating an anatomical-physiological theory of neural organization that will be as near physiological fact as possible and still capable of accounting for a wide range of normal and pathological behavioral phenomena. The theory deals with the roles of pain, emotion, hunger, sex, fatigue, and monotony in learning and with the mechanisms underlying pleasure, attention, sleep, and waking. The importance of learning in perceptual differentiation and problem solution is stressed. The pathological behavioral phenomena covered by the theory include (*a*) the relatively small

loss of learned behaviors resulting from unilateral lesions, (*b*) the resistance of thoroughly overlearned behavior to cortical damage, (*c*) the serious behavioral deficits that may result from small areas of active pathological change, (*d*) the slight effects produced by large, clean-cut lesions (such as lobectomies), (*e*) the effect of electroconvulsive shock and lobectomy on emotional disturbances, (*f*) the relatively small effect of large cortical lesions on performance on verbal and nonverbal intelligence tests, and (g) the fact that early injuries may prevent the development of some intellectual capacities that an equally extensive injury, at maturity, would not have destroyed. To account for all these phenomena, Hebb proposes a number of anatomical-physiological constructs, including growth of "synaptic knobs," "the cell assembly," "the phase sequence," "the conceptual complex," and "hypersynchrony." Hebb clearly recognizes that most of his physiological constructs do not presently lend themselves to direct experimental test, but he believes that his system offers a framework for organizing existent behavioral and physiological knowledge. Although a great part of the theory is, as Hebb himself states, difficult or impossible to test with existent techniques, it has already aroused widespread interest and is certain to stimulate a host of investigations. In addition, the book represents a major contribution to physiological psychology in terms of the numerous behavioral and physiological materials that are subjected to critical review and reinterpretation.

Fulton's book (12), *Functional Localization in Relation to Frontal Lobotomy*, adapted from the 1948 William Withering Memorial Lectures, summarizes physiological and psychological research on the frontal lobes. Although the book is largely beyond the scope of this review, the description in Chapter II of Jacobsen's (22) study of the behavior of two chimpanzees after bilateral frontal lobectomy and the relating of this research to Moniz' later surgical studies are of interest. The effect of frontal lobotomy on pain, anxiety, and intellectual functions as described by the researches of Rylander, of Freeman & Watts, of Koskoff, and of Falconer are reviewed, but the data lack the precision necessary for any final evaluation. Two cases of bilateral traumatic injury to the frontal lobes of man, the Phineas Gage case and a case reported by Ritchie Russell, are described, both giving the typical picture of lack of emotional restraint and motivational loss. The difference between the pronounced effects from trauma and the limited or negligible losses from clean-cut surgical lesions is outstanding and has been noted by others. Russell's hypothesis is cited that "as age advances, the frontal-lobe mechanisms provide an asset of diminishing importance," that "injury to the prefrontal lobes in young children should lead to a very obvious failure in mental development" but that "by early or middle adult life the frontal lobes have already done much of their work by conditioning and moulding the pattern of the behaviour responses of the dominant left parietotemporal area" (12, p. 100). This hypothesis is hardly supported by the existent cases (particularly, Penfield's and Hebb's case of early frontal injury) and must be regarded as merely personal conjecture.

Frontal Lobe Syndrome

The classical symptom of intellectual loss following frontal lobectomy in the monkey was first described by Jacobsen and associates (22, 23) and consists of loss or drastic impairment of the ability to solve delayed response problems and little or no deficit in performance on visual discrimination tests. The concept of the frontal syndrome in monkeys was extended by the work of Harlow & Johnson (17) and Settlage, Zable & Harlow (46) to include difficulty in the initiation of behavior and severe impairment of the ability to adjust rapidly when the animals are presented with a series of problems involving contradictory reactions to similar or identical stimuli. Recent data by Harlow, Meyer & Settlage (18) suggest that bilateral frontal preparations have more difficulty in the solution of oddity problems than do normal monkeys, and an unpublished study by the same investigators shows that such operations impair double-alternation performance by monkeys. Indeed, one might hazard that the solution of all difficult and complex problems by rhesus monkeys is impaired by bilateral frontal lobectomy, whether or not this deficiency is specific to the frontal lobes.

Recent studies have amply confirmed Jacobsen's (22) finding that bilateral frontal lobectomy very seriously impairs delayed response performance by monkeys. Researches from the Wisconsin laboratory (16) have demonstrated that normal monkeys are consistently superior to monkeys with large bilateral lesions of the frontal areas; the differences are statistically significant, and there is seldom, if ever, overlapping in performance between the individual members of groups of normal and operated animals. This separation is apparently maintained regardless of length of delay (16, 35) and regardless of any discovered systematic variation of the conditions of testing, including kind of stimuli and intertrial feeding (35), controlled perseveration of position (15), interpolation of other kinds of problems, use or avoidance of screens, and many variations in the techniques of problem presentation (16). Repeated testing over a period of more than three years failed to give any indication of recovery of this particular ability in a group of four operated rhesus monkeys. Warren & Harlow (52) extensively tested, and a year later retested (53) matched groups of normal and operated rhesus monkeys on extensive series of simple (object) and difficult (pattern) discrimination problems. Although the normal animals were usually superior to the operated animals with bilateral frontal lesions, the differences were slight and in all cases failed to be statistically significant. Thus, these results confirm and expand the original findings of Jacobsen (22).

In view of the importance attached to the influence of frontal lobe lesions in man on motivational and social traits, the lack of subhuman data on such problems is most unfortunate. We may note that Harlow & Settlage (19) in an earlier study found "frustration" to be at least as common in monkeys with frontal lobe lesions as in normal monkeys. More recently, Davis, Settlage & Harlow (11) studied the performance of normal monkeys and monkeys with frontal lesions on mechanical puzzles without food incentives. Although no significant differences were found between the two groups

either in "spontaneous" manipulation or puzzle solutions, the general approach may still prove useful in relating the effects of operations in subhuman subjects to effects found in human subjects.

There have been no published reports of the effects of bilateral frontal lesions on the behavior of chimpanzees since the studies on "Lucy" and "Becky" [(10) and see Fulton (12)], but Ackerly (1) quotes at length a most interesting personal communication from Lashley:

> Chimpanzees give a different picture [from the monkey]. Two animals, now about three years old, had prefrontal lobectomies at about six weeks. They have been at all times within the range of normal controls in their physical and behavioral development. Two adults with prefrontal lobectomy and one with orbital gyri removed have shown no demonstrable symptoms. There is no restless pacing and, although there is a suspicion of increased activity when they are in the large compound, the difference is unreliable. There has been no loss of capacity for delayed reaction. They have learned delayed matching in normal time. There has been no change in emotionality, including reaction to frustration. These animals have not yet been sacrificed and anatomic controls are lacking but I am confident that the lesions extend to the caudal limits of the granular cortex (1).

The difference between the monkey and chimpanzee is difficult to explain. It has been suggested that the chimpanzee has alternative ways of doing the delayed response—some representative symbolism, equivalent to a language function—which dispenses with a more kinesthetic frontal lobe action, but there is no evidence to support this. Even though Crawford *et al.* (10) pointed out that ability or inability of their chimpanzees to solve delayed reactions was a function of the particular test conditions, it would appear that the performance of the animals described by Lashley is superior to that of the operated animals previously tested. At present, certainly, the weight of evidence suggests that chimpanzees with bilateral frontal lobectomy suffer some deficits on formal learning tests, even though these may be considerably less drastic than those exhibited by monkeys.

It is by no means difficult to believe that chimpanzees may perform very efficiently on many formal learning tests after bilateral frontal lobectomy when one considers the very remarkable results obtained on human beings by the Columbia-Greystone Associates (33). Twenty-three psychotic patients were subjected to bilateral partial ablation of the frontal cortex. The lesions in most cases corresponded to one or more of Brodmann's cytotechtonic areas, and the estimated weight of tissue removed ranged from 11.8 to 73.5 gm. The performance of these patients and their matched controls was subsequently measured on a battery of 35 psychological tests. Although it was not possible to test all patients on all tests, very extensive psychological measurement was completed on 19 patients. The subjects were tested before operation, three weeks after operation, and four months after operation. Some additional data were obtained eight months postoperatively and one year after operation. The results of the psychological testing are summarized by Landis as follows:

No patient in this group of 19 operatees which we have studied had a real or permanent impairment of mental function brought about by the operation, which could be demonstrated in any way by our exhaustive psychologic test battery. In individual patients specific losses in the form of the marked decreases in scores did occur but these losses were, so far as we could tell, more than compensated for by other marked gains and hence did not lead to impairment (33).

In view of the sweeping nature of these startling findings the results on selected specific tests merit consideration. Although the control group exceeded the operatee group on the performance items of the Wechsler-Bellevue, there were no group differences that were statistically significant [H. E. King (33)]. This finding is not particularly surprising inasmuch as earlier studies have indicated that formal intelligence tests are ineffectual instruments for differentiating between normal and brain-injured subjects. On the Porteus Mazes the operatee group was significantly inferior to the normal group three months postoperatively, but the differences between the groups steadily decreased and were not significant either 4 or 12 months after the operation [H. E. King (33)]. These findings of temporary loss and subsequent recovery are entirely in keeping with the results reported earlier by Porteus & Peters (41) on the effects of frontal lobotomy.

Not one of a battery of grouping and sorting tests [patterned after Gelb and Goldstein's tests of "abstract behavior" and having elements of similarity to the Category Test described by Halstead (13)] showed significant decrease in mean score after topectomy, and none of these tests gave significant differences between normal and operated groups [W. R. King (33)]. Examination of individual performances gave some indication of difficulty in voluntary shift in sorting behavior (Weigl test) when area 46 was removed, and some restriction in the number of objects grouped together when area 9 was ablated. The 12-month retest indicated that difficulty involving shifting on the Weigl test did not persist (33, p. 304). In summary, the investigators reported that impairment or loss of a categorical attitude could not be regularly demonstrated and that, in fact, there was not a single instance of an over-all, clear-cut loss in the abstract attitude.

No over-all decrease in CFF[2] was found among the operatees, and no decreased intra-individual variability in CFF was found, contrary to reports by Halstead (13). Furthermore, the CFF changes were not related to any biochemical, hematological, or encephalographic changes; nor was there any evidence that they belonged in some combination with other psychological tests such as those that Halstead combined to form into a power factor [K. M. Young (33)].

The negative results reported for the above tests held also for all learning and intelligence tests carried out, including tests of retention, both recognition and recall, immediate memory, sustained attention, memory for objects, continuous addition and subtraction, and double alternation. The outstanding alteration produced by the operation was a decrease in self-referred and self-conscious anxiety and mental complaints, and the individual changes

in these traits were related to the degree of social recovery [M. Garrison (33)].

On the basis of careful statistical analyses of the individual Rorschach factors before and after operation, J. Zubin (33) has reported that the operatees showed a greater decline in reaction time than the normals. The Rorschach factors which tended to decrease were associated with anxiety, ambitiousness, conflict, and introspection, and the factors that tended to increase were those related to lessening of ambition and lowering of standards of accuracy.

In summary, it would appear that the data of the Columbia-Greystone research show an amazing sparing of learning and intellectual functions as measured by formal tests, a reduction in anxiety in a considerable number of patients, and loss of ambition and deterioration of social behavior in patients with large cortical lesions (33, p. 429).

Since the publication of the book *Selective Partial Ablation of the Frontal Cortex* (33), two clinical investigators long interested in problems of frontal lobe function have made factual and interpretive contributions (1, 5). Ackerly (1) describes the behavior, over a period of more than fifteen years, of his famous male patient (J. P.) and of Spurling's well-known woman patient, both of whom suffered from very extensive frontal lobe deficit, and he supplements these data with case histories of two of his patients following bilateral leucotomy. The two bilateral frontal lobectomies had been tested by Halstead, who had found both defective in the abstraction and power factors. Ackerly's subject gave a very inferior performance on Halstead's Category Test. Although Ackerly refuses to accept the negative findings of the Columbia-Greystone group and will not concede intellectual sparing after bilateral frontal deficit, he stresses, not impaired intellectual performance, but impaired social adjustment as the primary syndrome of prefrontal lobectomy; such an interpretation is not at great variance with that made by the Columbia-Greystone group, particularly if allowances are made for lesion size. Ackerly writes as follows:

> The evidence to date seems to point to the frontal lobes as the seat of distance awareness, anxious concern, and motivation. Drives leading to adequate motivation are essential to man in coping effectively with the world in which he finds himself. If the great nerve net enables man to develop, amplify, and elaborate the processes of thought and feeling in many conflicting directions, it may be that here lies the source of sustained tension. It may be that such tension is necessary to activate the energy producing systems of the organism to create these drives without which man cannot achieve self-realization as a successfully contributing social being (1).

Brickner (5) has recently reported clinical observations and encephalographic measurements made from 1940 to 1949 on his famous case (A) of bilateral frontal lobectomy and has presented an autopsy report illustrating the lesion and disclosing the addition of pathological tissue, a tumor adherent to the left frontal stump and an occipital lobe tumor. Though Brickner does not believe that these tumors could have been existent at the time of

his earlier observations, their presence cannot be disproved, and it must be remembered that Brickner in his first report mentioned symptoms, such as paragrammatism, that are not typical of any frontal lobe syndrome.

A considerable part of Brickner's paper is devoted to a critical review of the effects of the loss of frontal lobe tissue. Brickner ardently defends the concept of a "typical frontal lobe syndrome," and he supports this position by citing Rylander's (45) cases and by implying that his own case, that of Ackerly (1), and that of Nichols & Hunt (36), who stated that there was residual tumor tissue remaining, were uncomplicated. He ignores the fact that Rylander was unable to define his lesions anatomically. Brickner criticizes with considerable propriety the importance that Hebb (21) has attached to the negative symptoms of a single case, that of K. M. Brickner points out that Hebb did not meet his own elementary requirements of adequate clinical controls, and he gives evidence showing that K. M.'s educational, social, and general intellectual status was not adequately considered and given proper appraisal in terms of the extreme importance that Hebb gave to this single case. In fairness to Hebb it should be said that he did not state that the case of K.M. proved that there was no frontal lobe syndrome; Hebb merely emphasized that there was no unequivocal evidence to demonstrate the existence of a frontal lobe syndrome.

In attacking the position taken by the Columbia-Greystone associates, Brickner states:

> The Columbia-Greystone cases are the only ones in the literature without preexisting brain lesions in which "frontal lobe symptoms" have resulted from a relatively limited removal of frontal tissue. . . . The work of the Columbia-Greystone associates . . . seems to prove a direct relation between the amount of frontal cortex removed and the development of [frontal lobe] symptoms (5, pp. 312–13).

Brickner's conclusion is not in keeping with the Columbia-Greystone data, which indicate that three weeks after operation "the two patients with most damage had a larger per cent of gains and a smaller per cent of losses than those patients with medium or little damage," and that four months after operation "there is little evidence that the gross amount of damage differentially affects the marked changes in psychologic test performance" (33, p. 310). Actually, Brickner avoids any reference to the data which indicate that there are no losses in learning and intellectual performance. He implies that the authors were not cognizant of social and motivational deterioration, even though the psychiatric section clearly points out in the main text and in the summary that such loss did occur in the four cases with the largest frontal lesions. Furthermore, Zubin's Rorschach data support such an opinion about motivational loss, and Landis has indicated that motivational loss might have occurred even though it is not objectively indicated in the data obtained on the formal tests.

Brickner's syndrome of "typical frontal lobe symptoms" is never precisely defined in his paper. At times it would appear that intellectual loss is involved, including loss on psychometric tests. At other times it appears that

he is willing to limit the frontal lobe syndrome to affective, motivational, and social traits. His desire to demonstrate the existence of some frontal lobe syndrome is, however, clear at all times.

Some evidence for a frontal lobe syndrome involving intellectual loss and personality change is presented by Malmo & Shagass (32). An attempt to establish a syndrome of intellectual loss associated with frontal lobe lesions and specific to this localization has been attempted by Halstead (14) on the basis of very extensive studies on a large number of brain-injured patients over a period of two decades. On the basis of factor analysis, Halstead separates four factors of "biological intelligence" and finds that the *A* factor, the capacity for abstracting universals, and the *P* or power factor are "maximized in the cortex of the prefrontal lobes." He presents data showing that patients with frontal lobectomies are significantly inferior to patients with nonfrontal lobectomies on the Category Test. There is, however, no evidence to show that these two groups of patients have lesions of equal size or that they have, with equal frequency, bilateral lesions; indeed, it would be most surprising if the latter condition, a condition of paramount importance, were met. Without assuming that any definable intellectual function has been predominantly localized in the frontal lobes or without accepting a gradient theory of "biological intelligence," we can accept Halstead's factual data that frontal lesions produce, on the average, greater deficit on some kinds of tests than do other lesions.

Although Halstead gives particular emphasis to the efficiency of the Category Test as an instrument differentiating frontal from nonfrontal lobectomies and both operated groups from controls, he also presents data which indicate that severely neurotic patients differ as much from normal subjects as do nonfrontal lobectomies, and chronic disease and endocrine patients differ more. Such data cannot help but suggest that the test measures more than the "capacity for abstracting universals." Although Halstead emphasized that his various groups were equated for all important variables, it is difficult to believe that groups composed in large part by obstetrical cases as opposed to victims of chronic essential hypertension and brain lesions or disease could be precisely equated for period of hospitalization or age, or both.

Halstead's four-factor theory of intelligence has found no favor among psychologists, and his procedures would not conform to the standards of modern psychometricians. His classification of specific tests defies logic and receives no support from the findings of the Columbia-Greystone project. The theories of cortical function in which Halstead is interested are simple and straightforward and should be testable by rudimentary experimental designs if adequate cases and controls are available. The complex and evasive procedures which Halstead has described contrast with the simplicity of the fundamental, present-day problems of cortical localization of intellectual function. Although Halstead has done more work and amassed more data on human brain-injured subjects than any other single man, it will not be possible to make an accurate appraisal of his findings until he presents his data in a clear-cut, unequivocal manner.

In spite of the very significant advances that have been made in our knowledge of the effects of large bilateral prefrontal lesions on behavior, it is obvious that there still exist major gaps and lacunae in this field of information. The number of learning tests administered to the monkeys has been limited, and there is little information concerning effects of lesions on motivation and social behavior. No comprehensive survey of chimpanzee behavior following bilateral frontal lesions has yet been reported. No analysis has ever been made in which human bilateral frontal lobectomy cases have been compared over a long period of time with adequately matched normal subjects. The Columbia-Greystone study certainly suffered from the facts that the lesions were small at best and the lesions of no two subjects were identical. The grouping of subjects with nonidentical lesions leaves much to be desired. The cursory reviews of the literature would suggest that there is little correlation between the human and subhuman literature. If an orderly picture does not exist, it must mean that our data are inadequate or our preconceptions are wrong. Since the absolute and relative size of the prefrontal areas increases with position in the phyletic scale, one might assume that bilateral frontal lobectomy would produce more serious effects in man than in subhuman animals. The possibility remains, however, that the more intelligent animals are better able to cover up loss by new techniques of learning than are the lower animals, and we now know that even monkeys can vastly compensate, through learning, for many intellectual deficits produced by cortical lesions. The apparent greater learning loss in subhuman animals may be a function of more complete controls over the subjects, particularly their learning life history. It is possible that our tests on subhuman animals measure more adequately the limits of learning ability than do our tests of human beings. Tests on subhuman animals are carried out under rigidly controlled conditions, but brain-injured human subjects are often "encouraged" and given additional time or additional trials, thereby obscuring motivational loss which may well constitute a factor, and possibly the factor, primarily related to the integrity of some cortical areas. We know so little about intelligence in any animal that we can expect only disappointment if we construct fanciful names for performance on a particular test, such as "abstract thinking" or "immediate memory," and expect these constructs to generalize throughout the phyletic scale.

Posterior Association Area Syndrome

Two great silent or associative cortical areas are recognized in the primate brain, the frontal associative area, lying rostral to the motor areas, and a posterior associative area, anatomically less clearly defined but extending over considerable portions of the parietal, temporal, and occipital lobe. Description of this second area as the PTO[2] area or as the posterior associative area does not imply that it may not include two or more associative areas, each mediating a different intellectual function or cluster of functions. In view of our limited present-day knowledge of the cortical localization of

intellectual functions, a conservative theoretical position seems highly desirable.

A series of studies carried out at the University of Wisconsin using rhesus monkeys as subjects presents very strong evidence for the existence of a posterior association area syndrome. Warren & Harlow have published two papers (52, 53) showing that four monkeys with extensive bilateral lesions in the posterior silent areas made significantly more errors on visual discrimination learning problems than did either four matched normal monkeys or four matched monkeys with bilateral lesions of the prefrontal areas. In the first of these papers (52) it was found that the monkeys with posterior lesions made more errors than the other groups on both easy (object) discriminations and difficult (pattern) discriminations. After an additional postoperative year, during which the animals were constantly tested on other than discrimination tests, the animals with posterior lesions had regained the ability to solve the simpler visual discriminations, and their performances could not be differentiated from the other groups'. Three different classes (color, form, size) of difficult (pattern) discriminations continued, however, to differentiate the posterior lesion group from the other groups at a statistically significant level (53). Furthermore, unpublished data indicate that this deficit persisted for at least an additional year. The serious impairment in performance that the monkeys with posterior lesions suffered on visual discrimination learning tests did not extend to delayed response situations. Extensive tests involving measurement of delayed response performance under a wide variety of conditions (15, 16, 35) demonstrated that the monkeys with posterior associative area lesions were not differentiable from the normal monkeys; indeed, statistically significant differences in performance were never obtained. The monkeys with posterior associative area lesions were significantly inferior to normal monkeys on the relatively complex oddity tests (18) and were usually inferior to normal monkeys on a measure of double alternation (29).

Strong support for the existence of a posterior (parieto-temporo-occipital or PTO) syndrome is offered by a series of studies conducted at the Yerkes Laboratory. Blum, Chow & Pribram (4) demonstrated that bilateral PTO[2] lesions severely affected simple (color) and more difficult (pattern) discriminations and produced deficit in patterned string problem performance and performance on a conditional reaction. They report possible impairment on delayed response performance in two monkeys, but in view of the variability found in relatively naive normal monkeys, the evidence is far from convincing. It should be pointed out that most of the studies from the Yerkes Laboratory were exploratory in nature in that relatively naive animals were tested, usually for less than a year, and that a single problem rather than a group of problems was usually taken as representative of a class or a type of test. Evidence concerning localization of the posterior association syndrome within the PTO[2] area is presented in two very important studies by Chow (7, 8). A total of 12 immature rhesus monkeys served as subjects,

and lesions were produced in parietal, prestriate, and temporal regions, and in various combinations of these areas. The effect of bilateral destruction of the frontal eyefield was also measured. Detailed anatomical checks both of the cortex and the thalamus were made in these studies. Chow has effectively summarized his results as follows:

> In view of the lack of any deficit in our subjects with lesions mostly confined within the preoccipital region . . . and Lashley's similar results, the focus is further restricted by the present study to the lateral surface of the temporal lobe, and more specifically, to the region aroung the middle temporal gyrus.
>
> The parietal region can be ruled out as being focal or crucial in visual function by the data on subject 7 . . . a complete parietal lobe ablation, in which tissue from the central fissure to the lunate sulcus and from the longitudinal fissure to the temporal lobe was excised. The animal thus treated showed no visual handicap. This lesion also indicates that the mass of tissue removed is not the critical factor in the production of deficit. . . .
>
> Furthermore, this temporal focus of visual function seems to be exclusively confined to the cortex itself, and does not correlate with disruption of any thalamocortical system (7).

In the later publication he states: "The temporal focus of visual function appears to be confined to the cortex. Degree of damage to the thalamic relay and associative nuclei is not correlated with visual disabilities" (8). Chow has already mentioned that his negative findings following lesions in the preoccipital area are in keeping with data by Lashley (28), and these data find additional support in an unpublished manuscript by Riopelle & Ades.

Data from a number of rather scattered and limited reports suggest that a picture of more drastic learning impairment is obtained from temporal lesions involving the ventral or the medial surfaces of the lobe, or both. Blum, Chow & Pribram (4) describe one case of bilateral temporal lobectomy in the rhesus monkey which produced "deficit in visual discrimination learning, patterned string problems, conditional reaction, delayed reaction, and changes in taste preference, in food selection, and in tractability." Performance on the discrimination problems and string tests is, however, well within the performance range of the PTO[2] animals. Performance on the conditional reaction (which is somewhat similar to, but probably simpler than, the oddity problem) has not been demonstrated to depend upon the integrity of any particular cortical locus. Delayed reaction deficit was adduced because the monkey failed "to meet the criterion at 15 seconds without the screen, and also failed in an additional 500 trials at 5 seconds with the screen." Such performance in the case of a single animal cannot be accepted as absolute proof of deficit, and it actually represents a performance much superior to that typically made by monkeys with bilateral frontal lobectomies. Changes in taste preference, food selection, and in increased tractability and decreased fearfulness suggest an incomplete temporal syndrome as described by Klüver & Bucy (25).

Reference must be made to the experiments of Poirer (40), who measured

the effects of temporal lobe lesions on five macaques by means of learning tests. Bilateral temporal lobotomy produced no loss in the single case studied. All the other cases were partial bilateral temporal lobectomies. Complete loss on visual discrimination tests occurred in one subject, severe loss in another, and little or no loss in the remaining two. In accounting for the differences, Poirer states:

> The production of this visual agnosia appears to depend upon the bilateral destruction of area 19, and possibly also of area 18, in addition to that of the caudal and basal area of the temporal lobe, which is much more under the influence of the visual association cortex than its more rostral and dorsal part.

Poirer's statements concerning the involvement of the periparastriate area are unwarranted inasmuch as he did not destroy areas 18 and 19 bilaterally, and his conclusions concerning these areas are undoubtedly untrue in view of the data previously presented in this paper. His conclusions concerning possible differential localization in the temporal lobe merit consideration, even though the range of his learning tests and the duration of the testing program were too limited to be in any way definitive. In fairness to Poirer it should be pointed out that his primary interest was anatomical.

Stewart & Ades (48) reported that bilateral, seriatum removal of the superior temporal gyri in *Macaca mulatta* produced loss of a conditioned auditory response in a shuttle-box apparatus if the interoperation interval was six days or less. Bilateral destruction of the inferior temporal gyrus produced no loss even though the lesions were larger. Blum *et al.* (4) reported no loss on a learned auditory discrimination after bilateral lesions in the temporal lobe, but it is possible that the lesions in the superior temporal gyrus were not as complete as were those of Stewart & Ades (48). An important paper by Riopelle and associates (44) reports that monkeys, after bilateral temporal lobectomy, showed no loss on patterned string test problems but were able to learn specific discrimination problems. The operated monkeys, unlike the normal monkeys, showed no interproblem learning, i.e., they showed no improvement in ability to solve discrimination problems when tested on a series of 315 problems. This failure to show interproblem learning, also described as failure to form "learning sets," on the part of the temporal-lobectomized animals represents an extremely serious behavioral loss that should markedly impair or completely destroy effective learned performance by monkeys on a wide range of behavioral tests, including immediate discrimination reversal and oddity. Theoretically, a monkey should not be able to solve a problem in a single trial unless it can form learning sets, and the above tests require that the animal be able to learn or unlearn in a single trial.

The effects of bilateral temporal lobectomy are presented by Klüver (24), who summarizes the results obtained by himself and Bucy on monkey subjects and presents detailed descriptions of the nature and extent of the lesions. The symptoms described by Klüver are "psychic blindness" (involv-

ing the loss of ability to recognize and detect the meaning of objects on the basis of visual criteria alone), impulsive and indiscriminate oral examination of objects, a "hypermetamorphic impulse" to attend and tactually react to every visual stimulus, hypersexuality, and profound emotional changes even involving complete loss of fear and anger responses. Klüver also reports observations made by Brown & Schäfer (6) on two monkeys with bilateral destruction of the temporal lobes, and these observations, made more than fifty years earlier, agree in every important detail with those of Klüver & Bucy (25). Brown & Schäfer's published photographs of their monkeys' lesions were compared with, and found to be similar to, the lesions produced by Klüver & Bucy, which involved the inferior portions of the first and second temporal convolutions, the pole, and all but the posterior part of the hippocampal formation. Inasmuch as Smith (47) and Ward (51) had produced some similar symptoms in attenuated form by lesions in the rostral cingular gyrus, Klüver speculates that his temporal lobe syndrome may result from destruction of the hippocampal formation and its connections, and he discusses his results in terms of Papez' anatomical circuit elaborating and regulating functions of central emotion.

It is probable that the extreme visual deficit, "psychic blindness," represents an exaggeration of the less severe deficit imposed on visually guided learned behaviors by more circumscribed bilateral temporal lesions. As we have already seen, lesions involving either the lateral temporal surfaces or the caudal and basal temporal lobe areas may produce severe and prolonged agnosias. The existent data unfortunately are too scanty to enable us to come to any definitive answer concerning the size of lesion and severity of the learned visual deficit. At present, we cannot even tell whether or not destruction of, or damage to, the rhinencephalon imposes added quantitative or qualitative deficit to that produced by gross neocortical temporal lesions.

There has not appeared during these last four years any definitive evidence for a posterior association syndrome in man, but one would not expect clear-cut evidence of such a syndrome unless cases of bilateral posterior lesions are found. The classical pictures of visual and auditory aphasia and apraxia might be regarded as evidence of partial or highly specific posterior association syndromes. Nielsen's (24) differential syndromes of agnosia for animate objects and agnosia for inanimate objects are not fully supported by his anatomical data and are based on unsatisfactory behavioral tests.

Penfield's (37, 38) remarkable studies of evoked recollections from stimulation of the temporal cortex strongly suggest that these posterior areas are intimately associated with complex associative functions, visual as well as auditory, and probably integrative visual-auditory association.

Cortical Localization, Mass Action, and Equipotentiality

The original studies by Jacobsen and associates (22, 23) gave presumptive evidence for cortical intellectual localization. These studies have been extended and amplified by the work of Harlow and associates (15, 16, 35),

which appears to establish beyond reasonable doubt the existence of differential frontal and posterior association syndromes of intellectual loss in the rhesus monkey. Bilateral destruction of the prefrontal areas produces statistically significant loss on all known forms of delayed response tests and no statistically significant loss on easy or difficult discrimination tests. In contrast with the reports of Jacobsen *et al.* (22, 23), Harlow and associates (15, 16, 35) found that large bilateral lesions in the posterior association areas did not produce statistically significant loss on delayed response tests tests but did produce significant loss on discrimination tests—a loss that was temporary for simple discrimination and probably permanent for difficult discrimination tests. These data are, in general, supported by the findings of both Blum, Chow & Pribram (4) and Chow (7), who reported that large PTO[2] lesions (the region around the middle temporal gyrus probably being particularly important) produced serious loss in a battery of learned visual tests and no loss or questionable loss on delayed response tests.

Doubt that the efficiency of delayed response performance was drastically impaired only by frontal lesions was expressed by Lashley, who stated that four or five spider monkeys with bilateral prestriate lesions showed delayed response impairment. These findings were not confirmed in either of two studies by Chow (7, 8), using rhesus monkeys, or in a study by Meyer, Harlow & Ades (34), who also used rhesus monkeys as subjects. No animal in any of these investigations gave any indication of delayed response deficit. Blum, Chow & Pribram (4) reported impaired delayed response performance in one of four monkeys with bilateral damage to the PTO[2] areas and in one monkey with bilateral temporal lobectomy. In view of the limited testing experience of their animals, the lack of control groups, the extremely small size of the groups of animals with comparable lesions (one or two), and test-retest variability (16) on delayed response measures, the case of the PTO animal may be dismissed and judgment of the effect of temporal lobectomy held in abeyance.

Support for the theory of differential intellectual loss following lesions to frontal and posterior association areas is found in the study by Chow, Blum & Blum (9), in which they described the effect of the addition of bilateral destruction of the prefrontal area to bilateral destruction of the posterior associative areas. After the frontal lesions all four rhesus monkeys showed very drastic delayed reaction deficit whereas visual discrimination habits were unaffected. Similar results have been obtained by Harlow and coworkers in an unpublished paper. Bilateral frontal lesions were produced in two monkeys with bilateral posterior association lesions of two years' standing, and bilateral destruction of the posterior association areas was effected on two monkeys with long-established frontal lobectomies. The new posterior lesions produced drastic impairment on difficult discrimination tests but no additional deficit in delayed response performance, and the new frontal ablations resulted in serious impairment of delayed response performance and no additional deficit on difficult discrimination problems.

Description of differential syndromes of intellectual loss resulting from lesions in the frontal and posterior association areas of primates does not imply that all intellectual functions are localized solely in one of these areas. Some monkeys are able to perform on simple delayed response tests at a level significantly better than chance after frontal lobectomy, and no bilateral posterior lesion has ever been reported to destroy all ability to learn simple discrimination problems. Further indication that bilateral frontal lesions do not totally abolish delayed response capacity is found in the controversial studies concerning the effects of sedatives on learning. Wade (50) reported that two lobectomized animals solved 25-sec. delayed reaction tests under a 25 per cent anesthetic dose of barbiturates, and one animal continued to make correct responses after being "returned to the typical hyperactive state" (p. 194). Although similar results had previously been reported by Pribram (42) and Wade (49), the effect and mode of operation of sedative and excitant drugs on delayed response performance of monkeys with prefrontal destruction remain unsettled in view of the research of Blum, Chow & Blum (3). These investigators tested two rhesus monkeys with bilateral prefrontal lesions and two monkeys with combined lesions of the frontal and posterior association areas on delayed response performance under saline solutions, amphetamine, and two doses of pentobarbital. Although both pentobarbital and amphetamine reduced the hyperactivity of the monkeys, there was no concomitant improvement in either of the two groups under any drug condition. Blum, Chow & Blum have suggested that sedatives may hasten the process of postoperative improvement and adaptation "but that they have no effect on the associative process which must occur anew on each trial."

Behavorial deficits have also been reported from nonspecific cortical lesions. Thus, subtotal hemispherectomy in the rhesus monkey (13) produces temporary loss on discrimination, discrimination reversal, and delayed response performance and may produce permanent loss on oddity tests. Although the cases of human hemispherectomy have never been critically reviewed, it may be stated authoritatively that, in spite of the inadequacy of the behavorial, sociological, and psychiatric data in all reported cases, there is a strong indication of intellectual, social, and motivational loss. It is, of course, extremely unfortunate that detailed, exhaustive studies could not have been made on clear-cut human hemispherectomies and bilateral frontal lobectomies.

The data we have presented are strongly opposed to Lashley's theory (27) of equipotentiality of cortical function in that certain tests (and presumably kinds of intellectual abilities) are selectively affected to a statistically significant degree by differential localization of cortical ablations. It would be premature to suggest that such findings rule out cortical equipotentiality for all tests or all intellectual functions inasmuch as some tests, and conceivably all very difficult tests, are adversely and seriously affected by lesions in disparate cortical areas. Hemispherectomy apparently produces far more serious loss than unilateral destruction of either the frontal or posterior

association areas. Lashley's theory of cortical equipotentiality would require that sensory areas mediate intellectual as well as receptive functions. During the last year, two researches bearing on this problem have been reported (30, 39).

A position favorable to Lashley's theory that primary sensory cortical areas possess important extra sensory functions in the solution of problems has been presented by Levine (30) for one sensory area. Levine compared intelligence test performance of three groups of soldiers before and after blinding. One group of 118 was peripherally blinded, one group of 32 peripherally blinded and with a brain injury to an area other than the occipital, and the third group of 20 partially or completely blinded as a result of brain injury involving the occipital cortex. The cortically injured groups, and particularly the occipital group, were inferior to those suffering from peripheral blindness. Greatest loss in the occipital-lesion group came in the subtests of digit span and arithmetic; similarities, which might be considered a measure of "abstract thinking," was least affected. Levine concluded that notwithstanding the limitations of uncontrollable shortcomings, including lack of knowledge of the extent of the lesions, the research demonstrated that "the occipital cortex of man performs important intellectual functions."

Results unfavorable to the theory of equipotentiality of cortical function in learning were reported by Pickett (39), who tested rats in three different kinds of mazes designed to limit learning to kinesthetic-cutaneous cues. On narrow, elevated maze performances, anterior lesions produced significantly more deterioration than posterior lesions, but the differences may be attributed in part to motor impairment. Performance on the alley maze was not influenced by incoordination. When rats with anterior and posterior lesions were selected and matched for lesion size, no significant differences were found. The fact remains, however, that the size of the posterior lesions did not correlate with deterioration scores, but deterioration scores were positively and significantly correlated with size of anterior lesions. No evidence for significant loss from the posterior (nonsomesthetic) area of the cortex appeared, in contrast with Lashley's finding that lesions of the striate area of the cortex interfere with retention of an alley maze learned in the absence of vision. These facts led Pickett to conclude that his findings are inconsistent with Lashley's theory of equipotentiality of cortical function and to favor explanation in terms of involvement of cortical projection areas mediating essential sensory controls. Though Pickett attacks the theory of equipotentiality, he presents no data for the existence of any nonsensory associative cortical area or areas.

Separation of sensory, perceptual, and intellectual loss in any definitive manner is difficult, and perhaps impossible in many cases, for these functions, if indeed they are discrete functions, must interact in diverse and complex manners. The clear-cut demonstration that different portions of a single cortical area (frontal or temporal associative cortex) are unequally involved in the mediation of a specific learned or intellectual function would present

presumptive evidence against cortical equipotentiality. The data already presented on the temporal lobes suggest unequal importance of different temporal lobe areas in mediating visual learning tests, but the data do not differentiate the effect of size of temporal lobe lesion (mass action) from specific location.

More specific study of the problem was made by Blum (2), who tested the effects of subtotal frontal lobe lesion on six rhesus monkeys and obtained some evidence that "bilateral destruction of the tissue along the *sulcus rectus*, superiorly and inferiorly, produces the greatest deficit" and "the dorsal region [dorsal to *sulcus rectus*] is perhaps of greater importance than the ventrolateral." The best evidence on equipotentiality of cortical areas is presented in a well-designed and well-controlled research by Pribram *et al.* (43), who offer very strong evidence that lesions of the dorsolateral frontal lobe areas produce much more serious delayed response deficit than do lesions in the ventromedial portions of the frontal lobes. Although no localization data from the Columbia-Greystone project are definitive, we may note that lesions in the posterior portions of the affected lobe (areas 6 and 8) probably produced more transient loss than did lesions involving more rostral areas. These data also receive some support from the frontal lobe cases reported by Penfield (37).

An interesting related research is presented by Wade (50), who tested groups of two rhesus monkeys before and after prefrontal lobectomy, lobotomy, and circumsection, on latch-box, rake, delayed response, and conditional discrimination tests. Delayed response was the only test to differentiate the three groups, performance on this test being unaffected by circumsection and adversely affected by both lobotomy and lobectomy. Failure after lobotomy was attributed to "loss of interest in the situation," and after lobectomy to "hyperactivity."

Doubtless the most surprising, and possibly the most important, finding reported during the last three years is the amazing amount of recovery from intellectual loss occasioned by cortical lesions. Recovery from the effects of stationary lesions continues for a very long period of time and takes place for most and possibly all functions. This finding has abundant support from literature on both the human and subhuman species. Warren & Harlow (53) found recovery continuing in monkeys three and four years after bilateral posterior association area operations, and unpublished data show evidence of continuing recovery during the last (sixth) year of testing. Even in monkeys, training could not only compensate, but it could more than compensate, for the loss on many of the tests, particularly discrimination and discrimination reversal. These data are completely in keeping with those of the Columbia-Greystone (33) project, where in test after test original loss gradually disappeared with time and training, and early deficit frequently was replaced by performance superior to that found during preoperative testing. Neither of these studies is in any way an exception, for there is no case, either human or subhuman, where learning has not been reported, if

it was seriously attempted and tested, after stationary cortical lesions. The human and animal studies cited here differ from the other researches in the literature only in the magnitude of recovery.

Such data raise grave doubts that there is any stationary lesion which produces any deficit that cannot be partially alleviated by persistent and efficient training techniques. The data would appear to be almost overwhelmingly opposed to any theory of cortical localization of intellectual function which is anatomically precise or temporally static. It is, of course, no more surprising that cortically damaged animals can learn than that cortex-lacking animals, such as the flatworm and fishworm, can profit from experience.

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